OSU Oregon State University College of Pharmacy

Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 26, 2012 1:00-4:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070
Meeting Agenda

I. CALL TO ORDER 1:00 pm – 1:05 pm
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)

II. PROCESS 1:05 pm – 1:15 pm
- a. Review Procedure Document — M. Herink (OSU)
- b. EBM Review — D. Haxby (OSU)
- c. Approval

III. OLD BUSINESS 1:15 pm – 1:30 pm
- a. Methadone / LAO Drug Use Evaluation* — K.Ketchum (OSU)
  1. Proposed PA Criteria
  2. Public comment
  3. Discussion of clinical recommendations to OHA

IV. NEW BUSINESS 1:30 pm – 2:00 pm
- a. Dose Consolidation concept — R. Citron (OSU)
- b. Approval Pathway for New Drugs not in PDL classes* — R. Magrish (DMAP)
  1. Proposed policy
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA

BREAK 2:00 pm – 2:10 pm

IV. NEW BUSINESS (continued) 2:10 pm – 3:30 pm
- c. Oral Anticoagulants Abbreviated Class Review* — K. Sentena (OSU)
  1. Pradaxa (dabigatran)
  2. Xarelto (rivaroxaban)
  3. Public comment
  4. Discussion of clinical recommendations to OHA
- d. Hepatitis C New Drug Reviews* — S. Willard (OSU)
  1. Incivek (telaprevir)
  2. Victrelis (boceprevir)
  3. Public comment
  4. Discussion of clinical recommendations to OHA
- e. ACE-Is/ARBs/DRIs Class Update* — M. Herink (OSU)
  1. Edarbi (azilsartan)
  2. Public comment
  3. Discussion of clinical recommendations to OHA

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

f. Drug Class Scans* M. Herink (OSU)
   1. HSV Antivirals
   2. Influenza Antivirals
   3. Beta Blockers
   4. Calcium Channel Blockers
   5. Public Comment

V. EXECUTIVE SESSION 3:30 PM

VI. RECONVENE for PUBLIC RECOMMENDATIONS*

VII. FUTURE BUSINESS
Tentative Review Schedule and Prioritization

VIII. ADJOURN

Agenda items with an asterisk will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)

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OREGON PHARMACY & THERAPEUTICS COMMITTEE MEMBERSHIP REPORT

First Name	LastName	Title	Position	Date Began	Term Ends	DUR Office	Specialty/Practice Setting	Geography
Andris	Antoniskis	MD	Physician	Nov-11	Dec-12		Internal Medicine	Portland
Joshua	Bishop	PharmD	Pharmacist	Nov-11	Dec-14		Pharmacy Director	Bend
Zahia	Esber	MD	Physician	Nov-11	Dec-13		Internal Medicine	Eugene
Tracy	Klein	PhD, FNP	Public	Nov-11	Dec-14	Vice Chair	Nurse Practitioner	Portland
Phillip	Levine	PhD	Public	Nov-11	Dec-12		Retired	Lake Oswego
Meena	Mital	MD	Physician	Nov-11	Dec-14		Deputy Medical Director	Portland
William	Origer	MD	Physician	Nov-11	Dec-14	Chair	Medical Director	Corvallis
David	Pass	MD	Physician	Nov-11	Dec-13		Medical Director	West Linn
Stacy	Ramirez	PharmD	Pharmacist	Nov-11	Dec-13		Ambulatory Care/Community Pharmacist	Albany
James	Slater	PharmD	Pharmacist	Nov-11	Dec-14		Associate Pharmacy Director	Beaverton
Cathy	Zehrung	RPh	Pharmacist	Nov-11	Dec-12		Pharmacy Manager	Silverton

Created on 1/24/2012 11:54:00 AM
Modified on 1/25/2012

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Oregon Pharmacy & Therapeutics Committee
Thursday, November 17, 2011 2:00-5:00 PM
Barbara Roberts Human Resources Building Rm#137
500 Summer Street NE, Salem, OR
DRAFT Meeting Minutes

Members Present: Andris Antoniskis, MD; Joshua Bishop, PharmD; Zahia Esber, MD; Tracy Klein, PhD, FNP; Phillip Levine, PhD; Meena Mital, MD; William Origer, MD; David Pass, MD; Stacy Ramirez, PharmD; James Slater, PharmD; Cathy Zehrung, RPh
Staff Present: Dean Haxby, PharmD; Roger Citron, RPh; Megan Herink, PharmD, BCPS; Ann Hamer, PharmD, BCPP; Kathy Sentena, PharmD; Ted Williams, PharmD, BCPS; Valerie Smith; Trevor Douglass, DC, MPH; Richard Holsapple, RPh; Ralph Magrish, MPA
Audience Present: Shannon Beatty (Med Immune); Linda Krueger (Eli Lilly); Venus Holder (Eli Lilly); Deron Grothe (Teva); Jim Graves (BMS); Bob Viadorx (BMS); John Stockton (Astellas); Amy Burus (OSU/OHSU Cop); David Barba (Forest); Barry Benson (Merck); Anne Marie Licos (Med Immune); Jeana Colabianchi (Sunovion); Lori Howarth (Bayer); Kate Ryan (Astra Zeneca); Dave Barrows (Merck); Tom Barrows (Merck); Cheryl Fletcher (Abbott); Bruce Smith (GSK); Jim Hoover (Bayer); Kathy Kirk (OPMC); Kathy Hahn (OPMC); Don Stoches (Novartis); Trish McDaid-O'Neill (Astra Zeneca); Darlene Halverson (Astra Zeneca); James Mattencci (MSD); Paul Nielsen (Med Immune); Shane Hall (Purdue); Mike Willett (Pfizer)

I. CALL TO ORDER
- a. The meeting was called to order at 2:10 pm and introductions were made
- b. Presentation by Dr. Bruce Goldberg, Director OHA
- c. Presentation by Linda Grimms, Legal Counsel to OHA
- d. Conflict of interest declaration; no new conflicts were disclosed

II. ELECTION of CHAIR and VICE CHAIR
- a. Dr. William Origer was nominated to chair the committee

ACTION: Committee voted unanimously to appoint Dr. Origer as chair
- b. Dr. Tracy Klein was nominated as vice-chair of the committee

ACTION: Committee voted unanimously to appoint Dr. Klein as vice-chair

SUSPEND P&T MEETING

III. RULES ADVISORY COMMITTEE for TEMP RULES
- a. Minutes from this meeting were recorded separately

CONTINUE P&T MEETING

IV. PROCESS
- a. Members were asked to review a draft document and provide feedback at the next meeting

ACTION: No action at this time

DRAFT

V. PLANNING

b. Future meeting dates, times and locations were discussed

ACTION: Future meetings will be held on the last Thursday of each month beginning in January 2012 from approximately 1-4 pm in the SW Portland Metro area

VI. NEW BUSINESS

a. Dr. Sentena presented a new drug evaluation on Prasugrel. Public comment was offered by Linda Krueger from Eli Lilly.
b. Dr. Sentena presented new drug evaluation on Ticagrelor. Public comment was offered by Kate Ryan from Astra Zeneca.

ACTION: Committee approved prior authorization criteria after adding the following:

- Diagnosis codes for the approved drug indications
- Length of treatment allowed for up to 12 months
- Allow for continuation of therapy for 30 days after hospitalization
- Grandfather patients currently taking medications for 12 months
- Make Prasugrel 2nd line and Prasugrel 3rd line therapy

VII. REPORTS/ DUR ACTIVITIES

a. The committee did not review the Methadone / LAO Drug Use Evaluation (DUE); however public comment was offered by Kathy Kirk and Kathy Hahn from Oregon Pain Management Commission

The meeting adjourned at approximately 5:25 pm

DRAFT

Methadone – New starts @ doses ≥20 mg

Goals:

- Promote safe use of methadone upon initiation

Prescribing Recommendations

- Opioid naïve or patients receiving codeine preparations: start at low dose and increase slowly:
  - 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly
- Conversion from other opioids
  - Starting dose 2.5mg-5mg q8h; upward titration by 2.5 mg q8h no sooner than weekly
  - Use short-acting opioid for breakthrough pain until optimum dose reached.

See Oregon DUR Board newsletter at:
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume11/DURV11I2.pdf
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume5/5_5.html

Length of Authorization: Up to 1 year

Requires PA: Patients initiated on methadone (i.e. no previous claim within 90 days) on a daily dose of ≥ 20mg

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9 code.	
2. Has patient been continuously on opioids other than codeine over the past 90 days?	**Yes: Go to #3**	**No: Pass to RPH; Deny** (Medical Appropriateness) Opioid naïve or patients receiving codeine preparations should start methadone @ 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly
3. Is the total Morphine Equivalent Dose per Day < 200mg? Dose Calculator at: http://pharmacy.oregonstate.edu/drug_policy/prescriber_tools/Opioid_Conversion_Suggestions.pdf	**Yes: Pass to RPH; Deny** (Medical Appropriateness) Recomment initiat methadone @ 2.5mg - 5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly and use short-acting opioids for break-through pain	**No: Go to #4**
4. Is this patient terminal (< 6 months) or admitted to hospice?	**Yes: Approve for up to 6 months.**	**No**: Go to #5.
5. Is patient being treated for oncology pain?	**Yes: Approve for up to 6 months.**	**No: Pass to RPH; Deny** (Medical Appropriateness)

DUR Board Action: *11/17/11 (KK), 5/19/11KK), 3/17/11(KK)*
Revision(s)
Initiated: *1/1/12*

DRAFT

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Drug Use Evaluation: Long-Acting Opioids (LAO)

Summary

- The LAO prior authorization policy was successful in lowering both utilization and cost of LAOs
- The LAO prior authorization policy reduced LAO excessive dose and duplication rates
- The methadone dose limit reduced the number of patients on more than 100mg per day
- Approximately 50% of patients on any LAO exceed 120mg morphine equivalent dose per day.
- About 30% of patients on any LAO concurrently take a benzodiazepine
- 5% of all methadone patients are started without any previous LAO therapy.
- 46% of patients newly started on methadone, without previous LAO therapy, exceed 120mg morphine equivalents per day.

Drug Use Evaluation: Long-Acting Opioids (LAO)

The use of long-acting opioids (LAO) has been steadily increasing despite concerns over efficacy and safety. Medicaid prescriptions for opioids doubled between 1998 and 2003, accounting for approximately 4% of all Medicaid prescriptions by 2003.[1] With increasing use of LAO there has been a corresponding increase in morbidity, as illustrated by an increasing amount of emergency department (ED) visits. The Drug Abuse Warning Network (DAWN) studied ED visits from 2004-2008 and saw a 111% increase in visits related to nonmedical use of opioid analgesics. Methadone, oxycodone and hydrocodone use were associated with the highest number of visits. The non-medical use of benzodiazepines accounted for an 89% increase in ED visits for the same study period.[2]

The consequences of escalating opioid use was reflected in a report from the 2010 Oregon Prescription Opioid Poisoning Workgroup. In 2007 opioid related poisonings accounted for 22.3% of all medication and drug-related hospitalizations in Oregon. Deaths due to prescription opioids in 2008 represented 53% of all deaths due to poisonings by medications and drugs. Methadone poisonings increased 70-fold since 1997 and deaths due to methadone accounted for 33% of the deaths due to poisonings in Oregon in 2008. In 75% of the deaths due to methadone, patients had a history of substance abuse listed in their charts.[3] Other studies have demonstrated that 18-41% of patients using opioids for chronic pain, showed drug abuse behavior.[4]

Deaths associated with LAO have also been increasing. Some states have reported proportional increases in deaths with the number of opioids prescribed, however, this phenomenon is not consistent in other states with rising mortality rates. It is unknown if increasing LAO deaths are due to an increased distribution of opioids, higher doses, specific LAO or other factors.[5]

Adverse Effects and Safety Issues

The most common adverse effects with LAO treatment are gastrointestinal, headache, fatigue and urinary complications. More severe, but less common, consequences of LAO therapy include sedation, hypoventilation, hallucinations, and abdominal pain. Methadone has been associated with additional serious warnings, outlined in the methadone section. Chronic opioid use has also been shown to effect hormone levels, cause abuse and addiction, tolerance and hyperalgesia.[6]

LAO products include black box warnings for respiratory depression, inappropriate use and drug/alcohol interactions. Methadone prescribing information specifically warns against rapid-titration of methadone with consequential drug accumulation leading to respiratory and cardiac effects. Additionally, warnings of QTc prolongation and arrhythmias in patients on high doses of methadone, and less commonly on maintenance doses, are described.[7] Fentanyl prescribing also contains additional warnings of life-threatening hypoventilation, even in opioid-tolerant patients, due to peak fentanyl concentrations occurring between 20-72 hours of treatment and because of its high potency.[8]

Although rare, serious consequences of LAO therapy include death due to drug abuse and misuse issues. Opioid treatment guidelines identify personal or family history of alcohol or drug abuse as one of the strongest predictors of aberrant drug use.[6] Additionally, patients with comorbid psychiatric conditions and younger age have also been shown to be at increased risk of opioid abuse in some studies.[9]

Drug Interactions

Many LAO are prone to drug interactions due to metabolism via CYP enzyme metabolic pathways. Commonly LAO are used in combination with benzodiazepines, which also utilize the CYP3A4 enzyme system. Studies have shown that patients on LAO therapy, taking benzodiazepines, routinely show more harms than non-benzodiazepine users. Newly published guidelines from the Canadian Guideline for the Safe and Effective Use of Opioids recommend that patients on benzodiazepines, starting opioid therapy, undergo a tapering trial or proceed with opioids with a slow titration and at lower doses if the combination is necessary.[10] A pharmacodynamic study of a single dose of diazepam in patients taking methadone resulted in greater subjective effects, or drug "high", but no acute physiological effects were seen.[11] Other studies have noted increased sedation and deterioration of reaction time when methadone and diazepam were given together. A study using "abuse" conditions – 0 and 40 mg diazepam in addition to 100% and 150% normal opioid-assisted therapy doses in four methadone and seven buprenorphine patients, demonstrated evidence of respiratory depression in some patients. Patients on LAO therapy requesting benzodiazepines should be assessed for appropriate use, other substance abuse, and source of benzodiazepines and likelihood of high-risk behaviors. LAO prescribing information warns against combining benzodiazepines, and other sedatives, and that these combinations may result in respiratory depression, profound sedation, hypotension and coma. Alcohol has been shown to further decrease respiration resulting in fatal overdoses in patients taking LAO, benzodiazepines and alcohol together.[11]

Methadone

As outline above, specific attention has been focused on the adverse effect profile of methadone, with an increased number of poisonings and death in Oregon and nation-wide. A 2004 Substance Abuse and Mental Health Services Administration (SAMHSA) report concluded that methadone related deaths were often a result of combining the drug with other central nervous system depressants, such as benzodiazepines, alcohol and other opioids.[12] Methadone is known to cause QTc prolongation and cardiac arrhythmias at higher doses or when give with interacting drugs. A small case series found episodes of torsades de pointes in high dose methadone uses (>400mg/day). Another case series in patients taking lower doses of methadone (median 110 mg/day) found that 32% had QTc prolongation but no incidences of torsades de pointes.[13] A recent study of QTc effects in advanced cancer patients taking methadone, found clinically significant increases in the QTc interval in only 1.6% of patients at week 2 and no changes at weeks 4 or 8.[14] However, there has been criticism of how this study

measured the QTc changes in addition to other design flaws. [15] To minimize this risk methadone should not be given to patients at increased risk of cardiac disease, arrhythmias or presentation of a prolonged QT interval prior to starting methadone therapy.[13]

Methadone pharmacokinetics and pharmacodynamics further complicate its use, as it has an unpredictable half-life, ranging from 15-60 hours and up to 120 hours in some patients.[6] Additionally, it is generally accepted that the analgesic efficacy wanes before its corresponding half-life, lending itself to be re-dosed leading to drug accumulation.[16] Guidelines recommend starting opioid naïve patients on 2.5mg every 8 hours, titrating the dose no more than weekly. It is also recommended that when switching patients to methadone from other LAO, doses above 40mg not be used even in patients taking high doses of LAO. Patients taking other LAO may be incompletely tolerant to the effects of methadone and deaths have resulted when converting patients from other chronic, high-dose opioid treatment regimens.[7]

Drug use criteria for appropriate methadone use has been suggested in the literature.[17] Recommendations include:

- Naïve patients should be initiated at a low dose and increased slowly.
- Patients converting from other opioids should be initiated on no more than 40mg/day and titrated no sooner than weekly.
- Patients should be assessed for QTc risk especially at high methadone doses. Doses of 60-150mg/day are recommended thresholds.

Guideline Recommendations

Using LAO for cancer or end of life pain is widely accepted but treating chronic noncancer pain with opioid therapy is more controversial. Many pain guidelines advocate the use of LAO for chronic noncancer pain despite limitations in evidence, escalating use, abuse and potential for life-threatening adverse effects.[6,18] The Veterans Affairs/Department of Defense Guidelines state that there is good evidence that LAO are effective for continuous pain.[19] The Cochrane report concluded that there is data to support that there is clinically important long-term pain relief for patients taking opioids for more than 6 months.[20]

Guidelines and systematic reviews on using LAO for non-cancer pain cite that there is no clear evidence that a specific opioid has demonstrated superior efficacy or safety over another.[6,10,21] There is limited evidence on the safest and most effective way to initiate, titrate, transition and select LAO therapy. Guidelines recommend initiating opioids at a low dose and titrating the drug slowly, taking into account the specific pharmacokinetics of the drugs, in order to minimize adverse effects. No LAO has specifically been shown to be safer of more effective as initial therapy.[6] Although opioids are viewed as having no maximum dose, guidelines recommend not exceeding

200mg/day of oral morphine, or equivalent, in patients with chronic noncancer pain (table 1).[6,10]

Table 1. Morphine Equivalents

Morphine 120mg	Fentanyl 50mcg/day	Morphine 200mg	Fentanyl 83mcg/day
	Hydromorphone 30mg/day		Hydromorphone 50mg/day
	Oxycodone 80mg/day		Oxycodone 133mg/day
	Oxymorphone 40mg/day		Oxymorphone 67mg/day
	Methadone 40mg/day		Methadone 67mg/day

Literature Review

A recent retrospective claim analysis of chronic opioid therapy in patients with non-cancer pain in commercial insured and Arkansas Medicaid populations was preformed. Regression analysis was used to determine risk factors for emergency department visits (EDV) and alcohol- or drug-related encounters (ADEs). ED visits were more commonly associated with younger age, females, more medical comorbidities, presence of headaches and greater number of nontracer pain conditions (less common pain conditions not specifically tracked). Opioid doses >120mg/day ME was associated with more ADEs but only statistically significant in the commercial insured population. In the Medicaid population the use of Schedule II long-acting drugs, alone or with non-Schedule II drugs, was significantly associated with more ADEs. Statistically significant RR increases in ADEs were seen with alcohol and/or nonopioid drug abuse or dependence in the Medicaid population. Combining sedative and/or hypnotic drugs with prescription opioids were also associated with ADEs and ED visits.[22]

In an additional analysis of the same populations, risk of possible and probable opioid misuse was performed. Twenty percent of the Medicaid population using chronic opioids were estimated to be misusing the drugs and 3% were probably misusing. The most common factors associated with misuse was younger age, back pain, multiple pain complaints, and substance abuse disorders. High dose opioids (>120 mg MED) and short-acting Schedule II opioids were also associated with misuse. There were also correlations between misuse and increasing numbers of prescribers and pharmacies.[9]

Additional studies of health plans have showed increased utilization of LAO for chronic noncancer pain. A study by Boudreau et al found that along with increased utilization there were also 28.6%-30.2% of plan members also using sedative hypnotics concomitantly with opioids.[22] Another study looking at opioid prescribing from 1991 to 2007 found an 850% increase in the number of oxycodone prescriptions, in which 28% were for long-acting oxycodone. There was a 5-fold increase in the number of oxycodone related deaths over the same period.[23]

Drug Use Evaluation: Long-Acting Opioids (LAO)

Drug Use Evaluations

In response to LAO safety concerns, Oregon FFS Medicaid LAO drug use was evaluated from January 2000 through December 2004. A retrospective observational study of 5684 patients with prescriptions for at least 28 days were analyzed. First reported adverse outcome among patients with new prescriptions for methadone, extended-release (ER) oxycodone, morphine ER, or transdermal fentanyl were documented. Patients in the oxycodone ER cohort were 35% less likely to have an event compared to the morphine ER cohort. Patients taking fentanyl for non-cancer pain had a higher risk of emergency department (ED) encounters compared to morphine ER. Patients with non-cancer pain taking methadone had a 57% increased risk of having symptoms of overdose compared to the morphine ER cohort. However, subjects taking methadone were less likely to be hospitalized than those taking morphine ER.[24]

More recently, methadone use in the Oregon FFS Medicaid population was analyzed. Drug claims from December 2007 through November 2008 in 1,045 patients showed 10% of the population taking methadone doses associated with QTc prolongation. Doses >120/day are known to cause QTc changes, putting patients at increased risk of sudden death. In 39% of new methadone users there was no record of prior claims for opioid medications and average daily doses were 47mg, exceeding recommendations for new starts and conversion from other opioid therapies. [17]

New policies were adopted to address these concerns regarding the safety risks associated with methadone and LAO use:

1. A prior authorization for Methadone doses > 100mg/day was implemented 1/1/10.
2. RetroDUR letters were sent to prescribers of methadone > 40mg/day, starting early 2010.
3. A prior authorization for non-preferred LAO was initiated, focusing on dose and duplication issues, for patients with OHP coverage on 7/1/2009.

The effectiveness of these policies were evaluated.

Methods

Trend analysis

A LAO was defined as an opioid drug that can be dosed one or two times daily. LAOs include fentanyl patches, levorphanol and methadone as well as long acting formulations of morphine, oxycodone, oxymorphone and morphine combined with naltrexone. See Appendix A for complete list of Generic Sequence Numbers used to identify these drugs.

Paid, clean, fee-for-service pharmacy claims from January 1, 2009 thru December 31, 2010 were queried for trends in LAO costs and utilization and quantified as a monthly per member per month (PMPM) value. Costs were defined as ingredient cost (paid

amount + copay amount + other insurance paid – dispensing fee) and utilization was defined as the claim count. Rebates were not included in the reported costs. Total eligibility figures for BMH (OHP Plus) and KIT (OHP standard) benefit packages were used for the denominator. Finally, total and average costs for 30 days were quantified during the pre-intervention period (1/1/09 - 6/30/09) and post intervention period (7/1/10-12/31/10).

LAO User Analysis
For pre-intervention period (1/1/09 – 6/30/2010) and the post-intervention period (7/1/10-12/31/10), LAO users were identified if a single claim was paid for a LAO. Each LAO user with at least 90 continuous days of therapy was included in the chronic use cohort. Continuous therapy is defined as sequential claims where the beginning of the next claim is no greater than 14 days after the end of the previous claim. The "end" of a claim is defined as claim date + day supply. Demographic information such as age, sex, and race were quantified in all LAO users as well as the chronic use cohort.

The prevalence of patients on more than one LAO was characterized pre- and post-intervention. The average dose and number of subjects exceeding 120mg of morphine equivalent per day (MED) was also described pre- and post intervention. Finally the number of patients exceeding 100mg per day of methadone was quantified pre- and post interventions. Dose calculations are included in Appendix A.

Duplicate LAO use was defined claims for two unique LAO with a continuous overlap of at least 60 days. This analysis was done in chronic users pre- and post- intervention. Additionally, those chronic LAO users on 60 days concurrently with drugs of concern (benzodiazepine, skeletal muscle relaxants and drugs affecting the QTc interval) were quantified. The complete lists of drugs of concern is in Appendix B.

The number of opioid naïve patients initiating methadone was quantified in the post period. This included any patient starting on methadone with no LAO in the previous 90-days. Patients in this analysis were restricted to those with >75% eligibility for the period.

Among the chronic users the prevalence of diagnoses thought to be common for LAO users was characterized. Specifically, ICD9CM codes from paid, clean, FFS or FCHP medical claims within 6 months prior of an index LAO claim were used to quantify the number of patients with conditions known to be treated with LAOs. A patient may have more than one condition of interest.

Results

Trend Analyses
From January 1, 2009 to December 31, 2010 utilization of LAO trended steadily downward (Figure 1). When the trend is examined for the three independent segments of pre-intervention, post LAO prior authorization (PA) and post methadone dose limit there is a discernable reduction in use temporal to the policies. The LAO PA affected all LAOs except generic long-acting morphine, methadone and levophanol and was

started July 1, 2009. It requires a covered OHP diagnosis and limits duplication and excessive dose. The LAO PA reduced use by 32% annually. Methadone doses exceeding 100mg required PA starting January 1, 2010. A RetroDUR intervention targeted doses greater than 40mg for education began in Q1-2010. There does not appear to be an additional reduction in response to the methadone policies. The trend is downward in all drugs with no apparent increases from drugs requiring PA to those that do not. One confounding factor is the increase in denominator overall during the same time period due to increasing enrollment which may account for the general downward trend in use PMPM.

Figure 1 - LAO Utilization PMPM (x10,000) 2009-2010

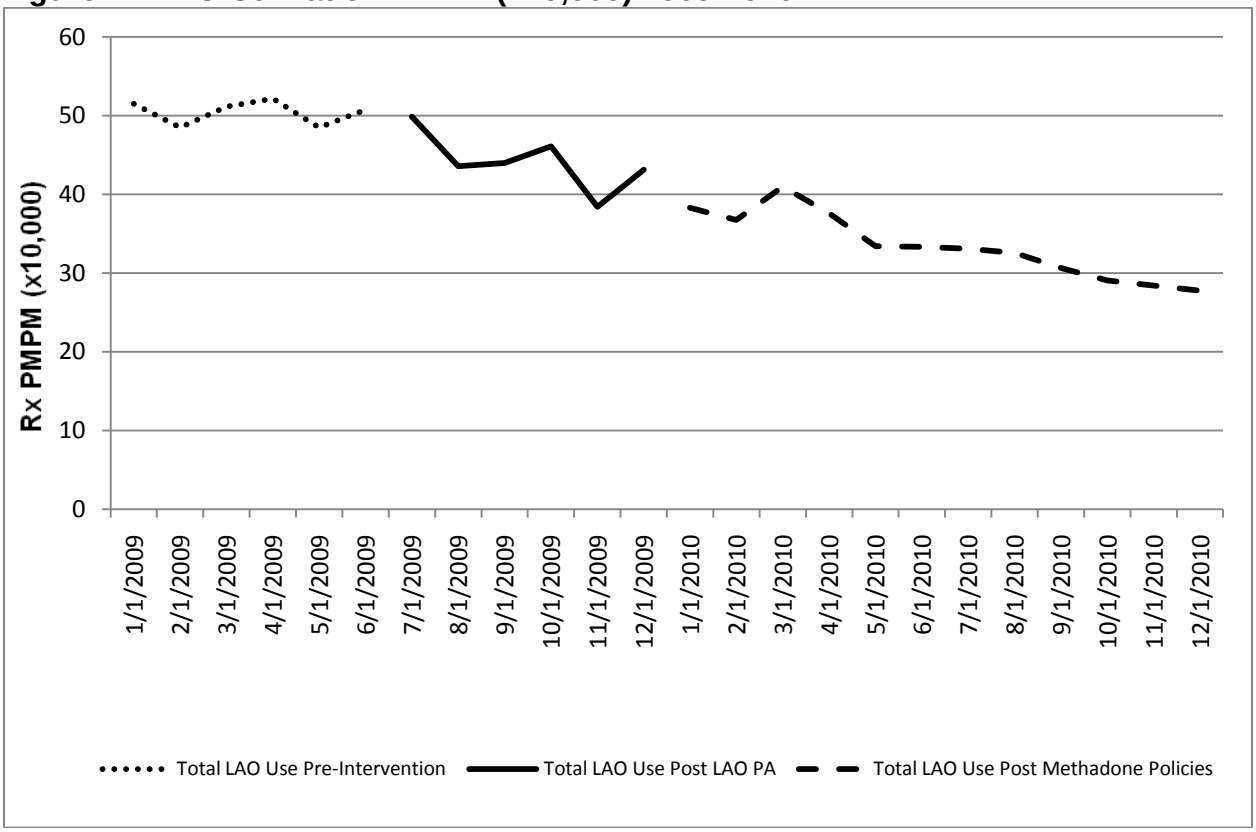
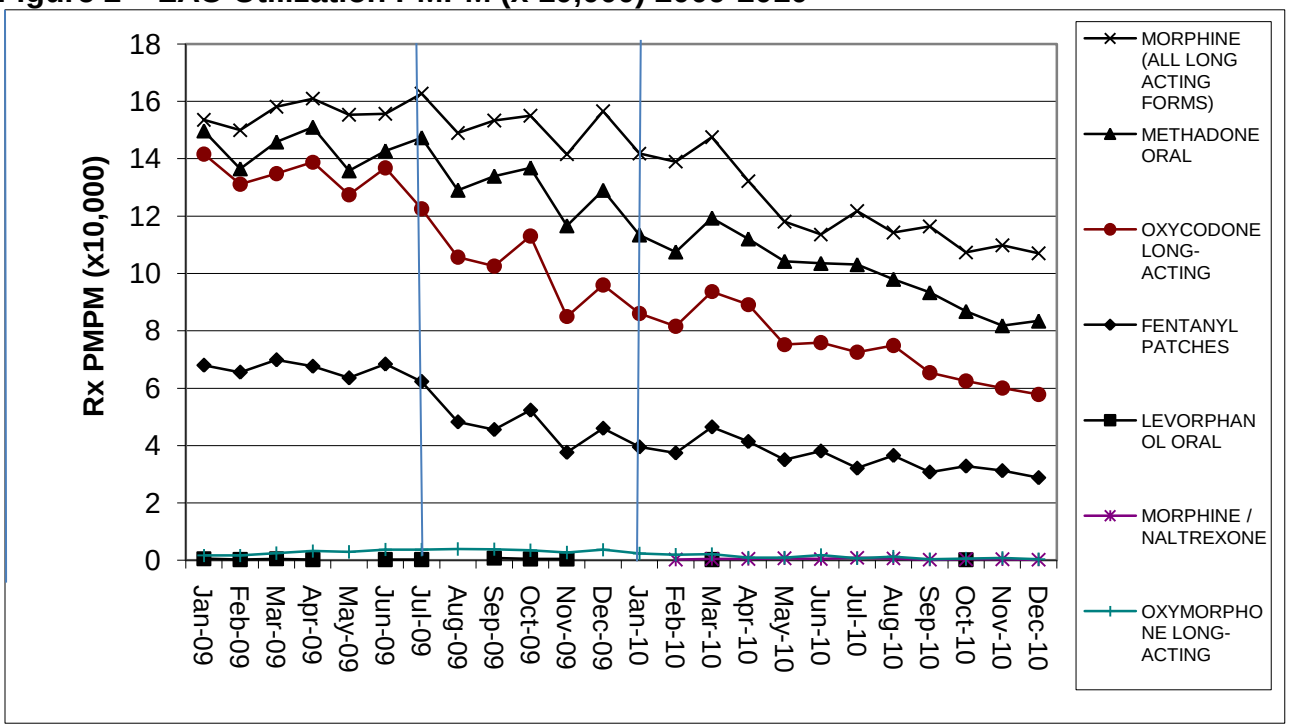
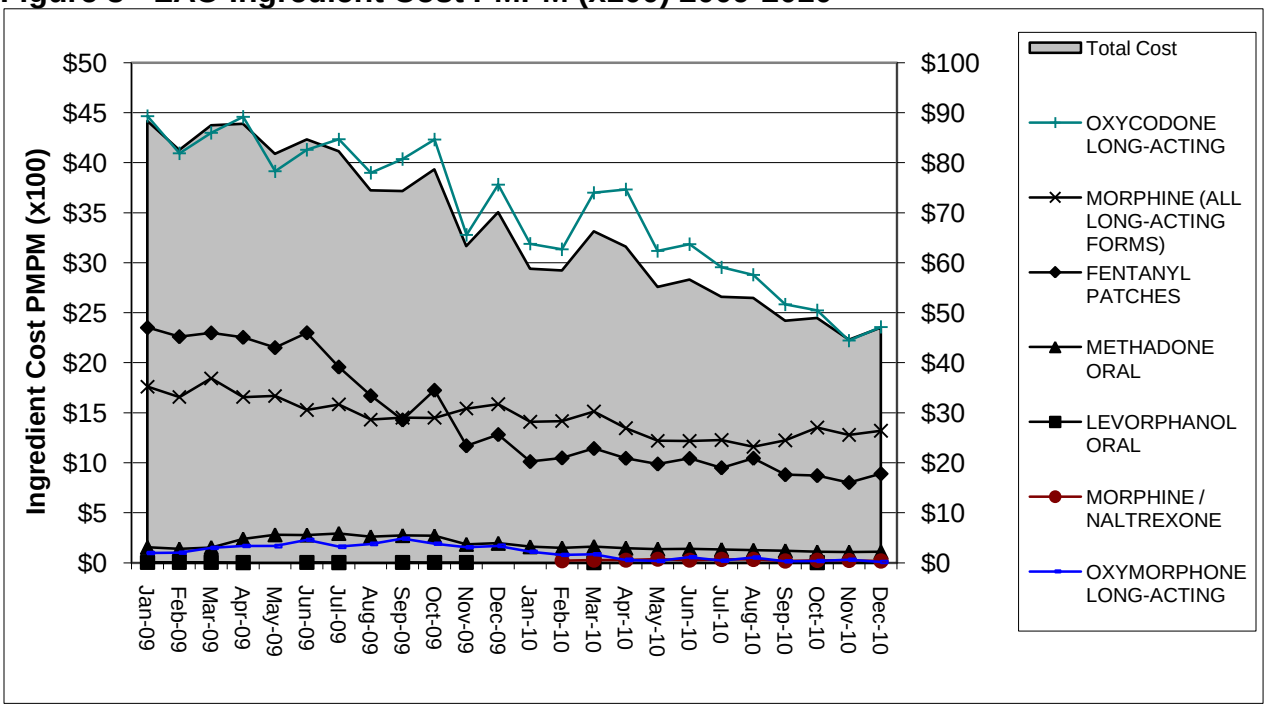


Figure 2 – LAO Utilization PMPM (x 10,000) 2009-2010



There is a similar downward trend in LAO PMPM costs with the total cost curve primarily following the oxycodone long-acting curve (Figure 3). Table 1 confirms that long-acting oxycodone is the primary cost driver. It captures 52.5% of the total gross drug costs while ranked 3rd by utilization (Figure 2).

Figure 3 - LAO Ingredient Cost PMPM (x100) 2009-2010



Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 1: Oregon FFS LAO Cost Summary

	% Change Pre-period to Post-Period		Post Period Costs		
	PMPM Utilization (x10,000)	PMPM Cost (x100)	Total Cost	(%) Total LAO Costs	Avg Cost / 30 Days
FENTANYL PATCHES	-52.4%	-60.1%	$255,723	18.4%	$325
LEVORPHANOL ORAL	-88.9%	-95.1%	$46	0.0%	$195
METHADONE ORAL	-36.7%	-43.7%	$33,138	2.4%	$16
MORPHINE (ALL LONG-ACTING FORMS)	-27.7%	-25.1%	$356,573	25.7%	$122
MORPHINE / NALTREXONE			$7,084	0.5%	$646
OXYCODONE LONG-ACTING	-51.6%	-39.0%	$727,972	52.5%	$473
OXYMORPHONE LONG-ACTING	-73.2%	-84.3%	$6,772	0.5%	$339
			$1,387,308		**$189**

LAO User Analysis

A total of 2273 unique patients had at least one claim for an LAO in the pre-intervention period of which 1437 (63%) were considered a chronic user of an LAO. During the post intervention period there were 1690 unique LAO patients identified and 941 (56%) were considered a chronic user. The demographics, shown in table 2, suggest that chronic users were similar to all users in terms of measurable patient characteristics. The mean age was ~48 years, however the range was from the very young (<1) to the very old (91). Most LAO users are in the 19-65 age group. There is perhaps a more prevalent LAO use among American Indians than the overall OHP population which is reported at just 1.8%.

Table 2: Demographics of all LAO users and chronic users

	Pre - Period				Post - Period			
	All Users		Chronic Users		All Users		Chronic Users	
Total	2,273	(%)	1,437	(%)	1,690	(%)	941	(%)
Mean Age	47		48		48		49	
Range	1-91		4-91		0-77		12-67	
<6	5	0.2%	1	0.1%	4	0.2%		0.0%
6-12	4	0.2%	1	0.1%	1	0.1%	1	0.1%
13-18	9	0.4%	5	0.3%	7	0.4%	3	0.3%
19-65	2,244	98.7%	1,424	99.1%	1,672	98.9%	933	99.1%
>65	11	0.5%	6	0.4%	6	0.4%	4	0.4%
Female	1,421	62.5%	904	62.9%	1,045	61.8%	591	62.8%
Race								
White	1,943	85.5%	1,227	85.4%	1,414	83.7%	805	85.5%
Am.Indian	153	6.7%	117	8.1%	157	9.3%	85	9.0%
Black	45	2.0%	20	1.4%	27	1.6%	13	1.4%
Asian	5	0.2%	3	0.2%	6	0.4%	3	0.3%
Other	127	5.6%	70	4.9%	86	5.1%	35	3.7%

Most chronic LAO users were taking long-acting forms of morphine followed by methadone. A market share shifted from both oxycodone long-acting and fentanyl patches toward morphine can be detected in this table. There was a 1% increase in the number of patients on methadone. Table 3 summarizes the distribution of specific LAO use.

Table 3: Distribution of LAO users pre- and post- interventions

Drug	Pre-Period% All Users	Post-Period % All Users
MORPHINE (ALL LONG-ACTING FORMS)	33%	41%
METHADONE ORAL	34%	35%
OXYCODONE LONG-ACTING	28%	19%
FENTANYL PATCHES	14%	10%
OXYMORPHONE LONG-ACTING	1%	0%
MORPHINE / NALTREXONE	0%	0%
LEVORPHANOL ORAL	0%	0%
Total	100%	100%

Table 4 depicts the average dose per day for each drug. With the exception of oxycodone and the naltrexone combination product the average dose declined or remained constant in the post-intervention period. The table also identifies the number of patients exceeding 120 mg MED before and after the interventions. The absolute numbers declined across the entire class but percentages remain concerning with 50% or more of patients on LAO exceeding the 120mg MED per day. Finally, the number of patients exceeding 100mg per day of methadone declined both in absolute numbers and percentage of patients on methadone.

Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 4: Dose Analysis of Chronic LAO users

	Pre - Period					Post - Period				
Drug	Avg Daily Dose (mg)	Patients >120mg ME/ day	(%) of patients on drug	Patients >100mg / day	(%) of patients on drug	Avg Daily Dose (mg)	Patients >120mg ME/day	(%) of patients on drug	Patients >100mg / day	(%) of patients on drug
FENTANYL PATCH TD72	2	37	16%			2	15	15%		
LEVORPHANOL TABLET	9					-				
METHADONE ORAL CONC	73	3	75%	1	25%	10				
METHADONE SOLUTION	58	1	50%	1	50%	30				
METHADONE TABLET	62	309	60%	110	21%	56	184	57%	29	9%
MORPHINE CAP ER PEL	139	14	50%			142	8	53%		
MORPHINE CPMP 24HR	134	5	33%			120	1	50%		
MORPHINE TABLET ER	142	212	42%			140	134	38%		
MORPHINE / NALTREXONE CAP ER PEL	40					120	1	50%		
OXYCODONE TAB ER 12H	90	202	47%			101	107	50%		
OXYMORPHONE TAB ER 12H	62	14	88%			37	2	67%		

Tables 5a and 5b compare 60 day duplication of LAO therapy pre- and post intervention. Prior to the intervention 6.7% of fentanyl patch users also used methadone concurrently, 5.1% used long-acting oxycodone concurrently and 2.8% used long-acting morphine concurrently. No other combinations exceeded 2%. Fentanyl patch users remain the only group that duplicated LAO by more than 2% in the post period but rates reduced to 3.3% with methadone, 2.2% with long-acting oxycodone and 3.3% with long-acting morphine. Absolute numbers were <3 for each combination in the post period.

Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 5a: Prevalence of concurrent LAO drugs among chronic users in the PRE period (n=1437)

	FENTANYL PATCHES (%)	LEVORPHANOL ORAL (%)	METHADONE ORAL (%)	MORPHINE (ALL LONG-ACTING FORMS) (%)	MORPHINE / NALTREXONE (%)	OXYCODONE LONG-ACTING (%)	OXYMORPHONE LONG-ACTING (%)
n	**178**	**1**	**446**	**416**	**0**	**372**	**10**
FENTANYL PATCHES		0 0.0%	12 2.7%	5 1.2%		9 2.4%	0 0.0%
LEVORPHANOL	0 0.0%		0 0.0%	0 0.0%		0 0.0%	0 0.0%
METHADONE	12 6.7%	0 0.0%		7 1.7%		5 1.3%	0 0.0%
MORPHINE (ALL LONG-ACTING FORMS)	5 2.8%	0 0.0%	7 1.6%			2 0.5%	0 0.0%
MORPHINE / NALTREXONE	0 0.0%	0 0.0%	0 0.0%	0 0.0%		0 0.0%	0 0.0%
OXYCODONE LONG-ACTING	9 5.1%	0 0.0%	5 1.1%	2 0.5%			0 0.0%
OXYMORPHONE LONG-ACTING	0 0.0%	0 0.0%	0 0.0%	0 0.0%		0 0.0%	

Table 5b: Prevalence of concurrent LAO drugs among chronic users in the POST period (n=941)

	FENTANYL PATCHES (%)	LEVORPHANOL ORAL (%)	METHADONE ORAL (%)	MORPHINE (ALL LONG-ACTING FORMS) (%)	MORPHINE / NALTREXONE (%)	OXYCODONE LONG-ACTING (%)	OXYMORPHONE LONG-ACTING (%)
n	**92**	**0**	**312**	**340**	**2**	**204**	**3**
FENTANYL PATCHES			3 1.0%	3 0.9%	0 0.0%	2 1.0%	0 0.0%
LEVORPHANOL	0 0.0%		0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
METHADONE	3 3.3%			2 0.6%	0 0.0%	2 1.0%	0 0.0%
MORPHINE (ALL LONG-ACTING FORMS)	3 3.3%		2 0.6%		0 0.0%	0 0.0%	0 0.0%
MORPHINE / NALTREXONE	0 0.0%		0 0.0%	0 0.0%		0 0.0%	0 0.0%
OXYCODONE LONG-ACTING	2 2.2%		2 0.6%	0 0.0%	0 0.0%		0 0.0%
OXYMORPHONE LONG-ACTING	0 0.0%		0 0.0%	0 0.0%	0 0.0%	0 0.0%	

Drug Use Evaluation: Long-Acting Opioids (LAO)

Table 6 indicates that there is a 29-34% incidence of 60-day concurrent use of LAOs with benzodiazepines, a 16-24% incidence of 60-day concurrent use of LAOs with skeletal muscle relaxants and 11-21% incidence of 60-day concurrent use of LAOs with drugs affecting the QTc interval.

Table 6: Chronic users with concurrent medications of concern in Post period

		Concurrent with:					
	Chronic Users	Benzodiazepine		Skeletal Muscle Relaxant		QTc Interval Drug	
Drug	n= 941	n=	(%)	n=	(%)	n=	(%)
FENTANYL PATCHES	102	32	31%	24	24%	20	20%
METHADONE ORAL	324	109	34%	64	20%	67	21%
MORPHINE (ALL LONG-ACTING FORMS)	371	107	29%	61	16%	67	18%
OXYCODONE LONG-ACTING	214	68	32%	40	19%	24	11%
OXYMORPHONE LONG-ACTING	3			1	33%		0%

Table 7 quantifies the number patients initiated on methadone with no prior LAO claim in the previous 90 days. There were 26 new patients that were LAO naïve. This represented 5% of all methadone users in the post-period. Of these, the average dose was 44mg per day. Sixteen patients exceeded 120mg MED and 1 exceed 100mg of methadone per day.

Table 7: New Methadone Starts in Post Period with no history of other LAOs in prior 90 Days

Total	**N=26**	**5% (all methadone users)**
Age		
Mean	45	
Range	19-62	
<6		
6-12		
13-18		
19-65	26	100%
>65		
Female	21	81%
Race		
White	21	81%
American Indian	4	15%
Black		
Asian		
Other	1	4%
Average Daily Methadone Dose	44mg	
Patients exceeding 120mg MED	12	46%
Patients exceeding 100mg methadone / day	1	4%

Diagnoses within the previous 6 months of an index claim for an LAO among chronic users in the post period are represented in Table 8. The most prevalent diagnosis present was dorsopathies.

Table 8: Presence of Pain Diagnosis in Prior 6 months, Chronic Users in Post Period only

		Chronic Users Post Period		
Pain Diagnoses	**ICD9**	n=	941	(%)
Cancer:	140x-239x		115	12.2%
Dorsopathy:	720x-724x		221	23.5%
Fibromyalgia:	7291		71	7.5%
Neuropathy:	350x-359x		66	7.0%
Osteoarthritis:	715x		96	10.2%

Discussion:

There has been a significant decrease in both the utilization and cost of LAOs since a prior authorization policy for the class was initiated on July 1, 2009 and a methadone dose limit and educational intervention was initiated on January 1, 2010. While the trend line is temporal to the PA policy, it is confounded by significant increases in OHP enrollment overall during the time period. However, absolute numbers have decreased in addition to PMPM trends and thus the policy likely had a significant effect on both use and cost.

Long-acting oxycodone remains the drug associated with the most cost despite losing 8% of patients between the pre- and post- intervention periods. Fentanyl patches also lost 4% market share by patient. Long-acting morphine gained 8% market share by patient and methadone gained 1%. This likely reflects the PA policy that exempted both long-acting morphine and methadone.

Several utilization markers of concern improved in the post- intervention period. Excessive doses remain with over 50% of users of most LAOs exceeding 120mg MED. However, absolute numbers have diminished. Methadone doses exceeding 100mg per day has declined from 110 patients (21%) to just 29 patients (9%).

There was also a reduction the concurrent use of LAOs. Patients on fentanyl patches remain the only patients that require duplicate LAO used in excess of 2% but absolute numbers are very low (<3). Finally, there appears to be a significant concurrent use (10-30%) of LAOs with drugs of concern for interaction. Benzodiazepines are the most prevalent.

Twenty-six patients (5%) were LAO naïve when initiated on methadone and the average dose exceeded 40mg per day. These clients are at the most risk for adverse outcome from methadone use.

Conclusions:
The LAO PA policy was successful in lowering both utilization and cost of LAOs. It has also improved LAO dosing and duplication. The methadone dose limit has improved methadone dosing. However, approximately 50% of patients on any LAO exceed 120mg MED. And, there is a significant incidence of concurrent use with drugs of concern, particularly benzodiazepines. Finally, over half of new methadone patients were started on doses exceeding 120 MED.

Recommendation:

- Consider adding LAO patients with concurrent use criteria for benzodiazepines or skeletal muscle relaxants to Pharmacy Lock-in Program (add current Lock-in Program screening criteria).
- Consider adding any patient the methadone dose limit *to* >40mg to Pharmacy Lock-in Program (add to current Lock-in Program screening criteria)
- Consider requiring a prior authorization for new methadone starts with no prior LAO use in last 90 days.

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Drug Use Evaluation: Long-Acting Opioids (LAO)

Appendix A

GSN	Generic Name	Strength	120mg Morphine Equivalent (ME)	Approx 120mg ME Disp Quantity / Day =	Max Dose / Day	Max Quantity / Day
15883	FENTANYL	100 mcg/ho	50 mcg / hr	0		
59102	FENTANYL	12 mcg/hou	50 mcg / hr	1.33333333		
15880	FENTANYL	25 mcg/hou	50 mcg / hr	0.66666666		
15881	FENTANYL	50 mcg/hou	50 mcg / hr	0.33333333		
15882	FENTANYL	75 mcg/hou	50 mcg / hr	0		
4228	LEVORPHANOL TARTRATE	2 mg	24 mg / day	12		
4240	METHADONE HCL	10 mg	40mg / day	4	100mg	10
4237	METHADONE HCL	10 mg/5 mL	40mg / day	20	100mg	50
4239	METHADONE HCL	10 mg/mL	40mg / day	4	100mg	10
23767	METHADONE HCL	40 mg	40mg / day	1	100mg	2.5
4242	METHADONE HCL	5 mg	40mg / day	8	100mg	20
4238	METHADONE HCL	5 mg/5 mL	40mg / day	40	100mg	100
60355	MORPHINE SULFATE	10 mg	120mg / day	12		
11886	MORPHINE SULFATE	100 mg	120mg / day	1		
60358	MORPHINE SULFATE	100 mg	120mg / day	1		
50219	MORPHINE SULFATE	120 mg	120mg / day	1		
11887	MORPHINE SULFATE	15 mg	120mg / day	8		
60356	MORPHINE SULFATE	20 mg	120mg / day	6		
16522	MORPHINE SULFATE	200 mg	120mg / day	0		
62358	MORPHINE SULFATE	200 mg	120mg / day	0		
4096	MORPHINE SULFATE	30 mg	120mg / day	4		
50222	MORPHINE SULFATE	30 mg	120mg / day	4		
61748	MORPHINE SULFATE	30 mg	120mg / day	4		
64739	MORPHINE SULFATE	45 mg	120mg / day	2.5		
60357	MORPHINE SULFATE	50 mg	120mg / day	2.5		
4097	MORPHINE SULFATE	60 mg	120mg / day	2		
50221	MORPHINE SULFATE	60 mg	120mg / day	2		
61749	MORPHINE SULFATE	60 mg	120mg / day	2		
64740	MORPHINE SULFATE	75 mg	120mg / day	1.5		
61722	MORPHINE SULFATE	80 mg	120mg / day	1.5		
50220	MORPHINE SULFATE	90 mg	120mg / day	1		
65549	MORPHINE SULFATE/NALTREXONE	100 mg-4 m	120mg / day	1		
65544	MORPHINE SULFATE/NALTREXONE	20 mg-0.8	120mg / day	6		
65545	MORPHINE SULFATE/NALTREXONE	30 mg-1.2	120mg / day	4		
65546	MORPHINE SULFATE/NALTREXONE	50 mg-2 mg	120mg / day	2.5		

65547	MORPHINE SULFATE/NALTREXONE	60 mg-2.4	120mg / day	2		
65548	MORPHINE SULFATE/NALTREXONE	80 mg-3.2	120mg / day	1.5		
24504	OXYCODONE HCL	10 mg	70mg / day	7		
63515	OXYCODONE HCL	15 mg	70mg / day	6		
24505	OXYCODONE HCL	20 mg	70mg / day	6		
63516	OXYCODONE HCL	30 mg	70mg / day	2		
24506	OXYCODONE HCL	40 mg	70mg / day	2		
63517	OXYCODONE HCL	60 mg	70mg / day	1		
25702	OXYCODONE HCL	80 mg	70mg / day	1		
61092	OXYMORPHONE HCL	10 mg	35mg / day	3.5		
63783	OXYMORPHONE HCL	15 mg	35mg / day	2		
61093	OXYMORPHONE HCL	20 mg	35mg / day	1.5		
63784	OXYMORPHONE HCL	30 mg	35mg / day	1		
61094	OXYMORPHONE HCL	40 mg	35mg / day	1		
61091	OXYMORPHONE HCL	5 mg	35mg / day	7		
63782	OXYMORPHONE HCL	7.5 mg	35mg / day	5		

Appendix B

Benzodiazepine List

GenName	HSN	RtCode
ESTAZOLAM	6036	PO
FLURAZEPAM HCL	1593	PO
MIDAZOLAM HCL	1619	PO
QUAZEPAM	1595	PO
TEMAZEPAM	1592	PO
TRIAZOLAM	1594	PO
ALPRAZOLAM	1617	PO
CLORAZEPATE DIPOTASSIUM	1612	PO
DIAZEPAM	1615	PO
LORAZEPAM	4846	PO
OXAZEPAM	1616	PO
CLONAZEPAM	1894	PO
TEMAZEPAM/DIET8	33614	PO
ALPRAZOLAM/DIETARY SUPPL NO.17	34747	PO

Skelatal Muscle Relaxants; any drug in STC = 08

Qtc Intx Drugs

GenName	HSN	RtCode
CLARITHROMYCIN	6228	PO

Drug Use Evaluation: Long-Acting Opioids (LAO)

ERYTHROMYCIN BASE	4022	PO
ERYTHROMYCIN ESTOLATE	4017	PO
ERYTHROMYCIN ETHYLSUCCINATE	4018	PO
ERYTHROMYCIN STEARATE	4021	PO
TELITHROMYCIN	23095	PO
ITRACONAZOLE	6503	PO
KETOCONAZOLE	4132	PO
POSACONAZOLE	33461	PO
VORICONAZOLE	23720	PO
AMIODARONE HCL	83	PO
QUINIDINE GLUCONATE	73	PO
QUINIDINE SULFATE	75	PO
ISONIAZID	4080	PO
ATAZANAVIR SULFATE	25390	PO
FOSAMPRENAVIR CALCIUM	25662	PO
INDINAVIR SULFATE	10683	PO
NELFINAVIR MESYLATE	10858	PO
RITONAVIR	10412	PO
SAQUINAVIR MESYLATE	10232	PO
ABACAVIR SULFATE/LAMIVUDINE	26524	PO
ABACAVIR/LAMIVUDINE/ZIDOVUDINE	21800	PO
DELAVIRDINE MESYLATE	12954	PO
EFAVIRENZ	18748	PO
ETRAVIRINE	35342	PO
LAMIVUDINE/ZIDOVUDINE	14014	PO
NEVIRAPINE	11592	PO
GATIFLOXACIN	20788	PO
LEVOFLOXACIN	12384	PO
MOXIFLOXACIN HCL	20690	PO
NORFLOXACIN	4123	PO
OFLOXACIN	6035	PO
CLOZAPINE	4834	PO
ILOPERIDONE	36778	PO
OLANZAPINE	11814	PO
PALIPERIDONE	34343	PO
QUETIAPINE FUMARATE	14015	PO
RISPERIDONE	8721	PO
ZIPRASIDONE HCL	21974	PO
ARIPIPRAZOLE	24551	PO
CHLORPROMAZINE HCL	1621	PO
FLUPHENAZINE HCL	1626	PO
PERPHENAZINE	1627	PO
THIORIDAZINE HCL	1631	PO

Drug Use Evaluation: Long-Acting Opioids (LAO)

TRIFLUOPERAZINE HCL	1630	PO
DRONEDARONE HYDROCHLORIDE	36444	PO
PROCHLORPERAZINE EDISYLATE	1628	PO
PROCHLORPERAZINE MALEATE	1629	PO
PROMETHAZINE HCL	12014	PO
CIPROFLOXACIN	13446	PO
CIPROFLOXACIN HCL	4124	PO
CIPROFLOXACIN/CIPROFLOXA HCL	32882	PO
AMITRIPTYLINE HCL	1643	PO
AMOXAPINE	1648	PO
CLOMIPRAMINE HCL	4744	PO
DESIPRAMINE HCL	1645	PO
DOXEPIN HCL	1650	PO
IMIPRAMINE HCL	1641	PO
IMIPRAMINE PAMOATE	1642	PO
MAPROTILINE HCL	1651	PO
NORTRIPTYLINE HCL	1644	PO
PROTRIPTYLINE HCL	1646	PO
TRIMIPRAMINE MALEATE	1649	PO

Opioids, Long-Acting – High Dose Limit

Goal(s):

- *Ensure safe use of long-acting opiods.*
  - *Opioids have been associated with an increasing proportion of deaths in Oregon and the US.*
  - *Opioid deaths in Oregon are often associated with concurrent use of other drugs (e.g. other opioids, benzodiazepines, skeletal muscle relaxants)*
  - *Opioid deaths in Oregon are often associated with patients with a history of drug abuse.*
- *Buprenorphine, Fentanyl and Methadone carry FDA Black Box Warnings and have been associated with adverse cardiac effects associated with QTc prolongation and/or life-threatening hypoventalation.*
  - *This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metablolism of methadone or fentanyl.*

See Oregon DUR Board newsletter at:
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume11/DURV11I2.pdf
http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/newsletter/articles/volume5/5_5.html

Initiative: Long-Acting Opioid High Dose Limit - Prior authorization is required for daily doses above the Dose Threshold in the table below. Patients with metastatic neoplasms (ICD9 = 190xx – 199xx) are exempt for the PA requirement.
Length of Authorization: up to 6 months

Dosing Threshold adapted from Washington State Agency Medical Directors Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain 2010 (www.agencymeddirectors.wa.gov)

Opioid	Dose threshold	Recommended starting dose for opioid-naïve patients	Considerations
Buprenorphine Transdermal	20mcg/hour (q 7 days)	5mcg/hr patch q 7 days	May increase dose q72 hours patients up to a max of 20mcg/hr q 7 days. Doses >20mcg/hr q7days increase risk of QTc prolongation.
Fentanyl Transdermal	50mcg/hour (q 72 hr)	Use only in opioid-tolerantpatients who have been taking ≥ 60mg MED daily for a week or longer	
Hydromorphone	30mg per 24 hours	2mg q 4–6 hours	
Methadone	80mg per 24 hours	2.5-5mg BID – TID	Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.
Morphine	120mg per 24 hours	Immediate-release: 10mg q 4 hours Sustained-release: 15mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80mg per 24 hours	Immediate-release: 5mg q 4–6 hours Sustained Release: 10mg q 12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000mg/day x <10day or 2500mg/day for 10 days or more)
Oxymorphone	40mg per 24 hours	Immediate-release: 5–10mg q 4–6 hours Sustained Release: 10mg q 12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol**.

Approval Criteria		
1. What is the patient's diagnosis?		
2. Is this patient terminal (< 6 months) or admitted to hospice?	**Yes: Approve for up to 6 months**.	**No**: Go to #3
3. Is patient being treated for oncology pain?	**Yes: Approve for up to 6 months.**	**No:** Go to #4

Comment [KLK1]: DUR Board recommended that any patient with claim with a "metastatic CA" diagnosis be excluded from PA altogether.

4. Is the diagnosis chronic back pain? (ICD-9 = 721.0, 721.2-721.3, 721.7-721.8, 721.90, 722.0 -722.6, 722.8-722.9, 723.1, 723.5-723.9, 724.1 -724.2, 724.5-724.9, 739, 839.2, or 847)	**Yes: Pass to RPh,** Go to #5.	**No:** Go to #6
5. Is there neurologic impairment defined as objective evidence of at least 1 of the following: a. Reflex loss b. Dermatomal muscle weakness c. Dermatomal sensory loss d. EMG or NCV evidence of nerve root impingement e. Cauda equina syndrome f. Neurogenic bowel or bladder	**Yes:** Document objective evidence with chart notes; Go to #8	**No: Deny.** (Not Covered by the OHP)
6. Is the diagnosis fibromyalgia (ICD-9 = 729.0 -729.2, 729.31-729.39,729.4-729.9 or V53.02)?	**Yes: Pass to RPh, Deny** (Not Covered by the OHP)	No: Go to #7
7. Is the diagnosis covered by the OHP?	**Yes:** Go to #8	**No: Pass to RPh, Deny** (Not Covered by the OHP)
8. Is this new therapy (i.e. no previous prescription for the same dose last month)?	**Yes: Pass to RPH; Deny** (Medical Appropriateness) In general, the total daily dose of opioid should not exceed 120 mg oral MED. Risks substantially increase at doses at or above 100mg.[1] Alternatives: Preferred NSAIDs or LAOs @ doses < 120mg MED.	**No**: Go to #9
9. Is the patient seeing a single prescribing practice & pharmacy for pain treatment?	**Yes: Pass to RPh,** Go to #10	**No: Pass to RPh, Approve 30-90 days to allow for case review.** Refer to Rx Lock-In program for evaluation, monitoring & potential taper. Further approvals pending RetroDUR/Medical Director review of case.
10. Can the prescriber provide documentation of sustained improvement in both function and pain AND is prescriber is aware of additional risk factors (e.g. concurrent benzodiazepines, skeletal muscle relaxants, other LAOs or history of drug abuse)?	**Yes: Approve up to 6 months.** **Quantity Limits Apply:** Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day	**No: Pass to RPh, Approve 30-90 days to allow for potential tapering of dose.** Refer to Rx Lock-In program for evaluation, monitoring & potential taper. Further approvals pending RetroDUR/Medical Director review of case.

Comment [KLK2]: DUR Board recommended that upon implementation all current patients be "grandfathered". This criteria will only apply to new patients to the OHP or new therapy.

[1] Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152(2):85-92

P&T or DUR Board Action: *11/17/11(KK), 3/17/11(KK), 5/19/11KK), 9/24/09(DO/KK), 5//21/09(KK)*
Revision(s) *1/1/12*
Initiated: *1/1/10 (Methadone only)*

Opioids - Long-Acting

Initiative: Long Acting Opioids for PDL

Length of Authorization: Up to 1 year

Approve use of non-preferred long-acting opioids only for covered diagnosis.

OHP does not cover:				
Disorders of soft tissue	*Includes ICD9:* *729.0-729.2, 729.31-729.39, 729.4-729.9, V53.02*	**OR**	**Acute and chronic disorders of spine without neurologic impairment**	*Includes ICD9:* *721.0 721.2-721.3 721.7-721.8 721.90 722.0-722.6 722.8-722.9 723.1 723.5-723.9 724.1-724.2 724.5-724.9 739 839.2 847*

Preferred Alternatives at doses below 120 Morphine Equivalent per day: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Non-Preferred LAOs require PA at any dose.

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9 code.	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA at doses below 120mg Morphine Equivalent per days.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Is patient being treated for oncology pain?	**Yes: Approve for up to 6 months**	**No:** Go to #4
4. Is this patient terminal (< 6 months) or admitted to hospice?	**Yes: Approve for up to 6 months.**	**No**: Go to #5.

5. Is the diagnosis chronic back pain ***721.0*** / ***723.1*** ***721.2-721.3*** / ***723.5-723.9*** ***721.7-721.8*** / ***724.1-724.2*** ***721.90*** / ***724.5-724.9*** ***722.0-722.6*** / ***739*** ***722.8-722.9*** / ***839.2*** ***847***	**Yes:** Pass to RPH, Go to #5.	**No:** Go to #**7.**
6. Is there neurologic impairment defined as objective evidence of at least 1 of the following: **a. Reflex loss** **b. Dermatomal muscle weakness** **c. Dermatomal sensory loss** **d. EMG or NCV evidence of nerve root impingement** **e. Cauda equina syndrome** **f. Neurogenic bowel or bladder**	**Yes:** Document objective evidence with chart notes; Go to #8.	**No: Deny** **(Not Covered by the OHP)**
7. Is the diagnosis fibromyalgia (ICD-9 = 729.0 -729.2, 729.31-729.39,729.4-729.9 or V53.02)?	**Yes: Pass to RPh, Deny** **(Not Covered by the OHP)**	No: Go to #8
8. Is the diagnosis covered by the OHP?	**Yes:** Go to #9	**No: Pass to RPh, Deny** (Not Covered by the OHP)
9. Is this new therapy (i.e. no previous prescription for the same drug last month)?	**Yes:** Go to #9	**No:** Go to #10**.**
9. Does dose exceed 120mg Morphine Equivalents per day? **a. Fentanyl 50mcg/day** **b. Hydromorphone 30mg/day** **c. Oxycodone 80mg/day** **d. Oxymorphone 40mg/day** **e. Methadone 40mg/day**	**Yes: Pass to RPh, Deny** (Medical Appropriateness) In general, the total daily dose of opioid should not exceed 120 mg oral MED. Risks substantially increase at doses at or above 100mg.[i] Alternatives: Preferred NSAIDs or LAOs @ doses < 120mg MED.	**No:** Go to #10.
10. Is the patient seeing a single prescribing practice & pharmacy for pain treatment?	**Yes:** Go to #11	**No:** <u>Approve 30-90 days;</u> Refer to Rx Lock-In program for evaluation, monitoring & potential taper. Further approvals pending RetroDUR/Medical Director review of case.

11. Is the patient concurrently on other long-acting opioids (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, long-acting oxymorphone)?	**Yes:** Pass to RPH. Go to #12.	**No: Approve up to 6 months.** **Quantity Limits Apply:** Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day
12. Is the duplication due to tapering or switching products? The concurrent use of multiple long-acting narcotics is not recommended unless tapering and switching products. Consider a higher daily dose of a single long-acting opioid combined with an immediate release product for breakthrough pain. http://www.ohsu.edu/ahec/pain/home.html	**Yes**: Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.	**No: Deny, Appropriateness.** **May approve for taper only.** If necessary, inform prescriber of provider reconsideration process and refer to RetroDUR for review.

P&T or DUR Board Action: *11/17/11(KK); 12/3/09 (KS), 9/9/09(klk),12/4/08klk, 3/19/09*
Revision(s): *1/1/12; 1/1/10*
Initiated: *7/1/09*

Prescription Opioid Overdose Prevention Workgroup (POP)
Interim Report
May 3, 2011

Executive Summary

OHA staff formed the POP in 2010 to determine how to reduce prescription opioid analgesic overdose deaths in Oregon. This report is an interim summary of information and recommendations from the Prescription Opioid Overdose Prevention Workgroup (POP). The POP formed four subcommittees to focus on data, education, policy, and clinical practice. The subcommittees considered three questions:

1. **What is the current state of knowledge for each specific POP areas of focus: data, policy, education, and clinical practice?**
   What is known about the frequency and risk factors for opioid overdose (data group)?
   What policies might contribute to the current state of affairs (policy group)?
   What education strategies have been employed (education group)?
   What do we know about the pharmacology of methadone and pain management practices (clinical practice group)?

2. **What questions do we still have unanswered?**
   What patient factors are likely to contribute to fatal overdose?
   To what extent have insurance reimbursement policies contributed to this problem?

3. **What are the next steps for each specific subject area (data, education, policy, and clinical practice)?**

Summary of Next Step Findings

- Need to reduce methadone overdose deaths - the cause of the majority of overdose mortalities occurring among Oregonians aged 25-54.
- Conduct a study to identify risk factors and circumstances among decedents.
- Identify healthcare provider education needs.
- Increase healthcare provider awareness of the efficacy of pharmacological and non-pharmacological pain treatment to relieve acute and chronic pain.

- Promote and disseminate standards for the use of opioids to relieve acute and chronic pain
- Encourage healthcare providers to use the Prescription Drug Monitoring Program beginning in September 2011.
- Assure that providers:
    - understand the side effects and risks of opioid use,
    - are knowledgeable about the use of medications used to treat opioid dependence,
    - Are able to recognize and screen for behaviors indicating potential substance abuse, and make appropriate referrals to addiction treatment providers.
- Develop and implement statewide public education and awareness focused on methadone misuse and overdose.
- Determine what best practice prescription opioid policies are needed to provide adequate patient management when using opioids to treat acute and chronic pain.
- Develop a policy recommendation that removes barriers and increases the availability and payment of Buprenorphine to treat chronic pain, opioid dependence and addiction.
- Develop a pilot project and test the usefulness of notifying primary care providers when a patients is referred to addiction treatment
- Develop a pilot project and test the usefulness of notifying the primary care provider when a patient dies of drug overdose.
- Develop a pilot project and test the usefulness of hospitals notifying the primary care provider when a patient is hospitalized for overdose.
- Develop a pilot project and test the usefulness of police notifying the primary care provider when a patient is cited or arrested on a drug charge.
- Develop survey questions for the Behavioral Risk Factor Surveillance Survey to determine what factors influence drug sharing and what factors might decrease this practice among Oregonians.

The POP will continue to meet monthly to coordinate OHA efforts.

Introduction

The Oregon Health Authority's (OHA) Addictions and Mental Health Division (AMH) and Public Health Division (PHD) formed the POP in 2010 to address prescription opioid analgesic overdose deaths in Oregon. A sharp increase in deaths related to opioid medications began in the late 1990's and continues to rise.

The POPP has two co-chairs, one from AMH, and one from PHD. The group consists of members from the OHA Division of Medical Assistance Programs (DMAP), OHA Addictions and Mental Health Division (AMH), Criminal Justice Commission (CJC), OHA Public Health Division (PHD), local health department representatives, Oregon Board of Pharmacy (OBP), Oregon Pain Commission (OPC), Advisory Commission for the Oregon Prescription Drug Monitoring Program, Kaiser Permanente, and the OHA Directors Office.

Methods

The POPP meets monthly to define and understand the scope of the problem (i.e. what is the magnitude and trend in overdose deaths, and what factors are associated with the increase in prescription opioid deaths). The POPP chartered four subcommittees to define the problem, explore current resources and practice, and examine evidence to formulate recommendations for the state. The subcommittee subject areas include: 1) data analysis, 2) clinical practice, 3) education; and 4) policy

Subcommittee Findings

I. Data

1. Deaths due to opioid analgesics have increased in Oregon.
   - Since 1999, prescription opioid overdose/poisoning deaths increased over 900%.
   - Between 1999 and 2009, there were over 1,250 prescription opioid; unintentional overdose/poisoning deaths in the state. Overall, this was a rate of 4.8 deaths per 100,000 persons in 2009.
   - Increases in hospitalizations also occurred. In 1997, opioid-related overdose/poisonings represented 5.6% of all medication and drug-related overdose/poisoning hospitalizations. In 2007, opioid-related

overdose/poisonings represented 22.3% of all medication and drug-related hospitalizations in Oregon.

- In 1999, prescription opioids represented 11% of all deaths due to overdose/poisoning by medications and drugs; in 2008, prescription opioids represented 53% of all deaths due to overdose/ poisoning by medications and drugs in Oregon.

2. The increase in opioid overdose deaths is primarily driven by methadone.
   - Methadone is commonly used to treat chronic pain, which accounts for much of its current use.
   - Methadone is more frequently mentioned on overdose death certificates than any other licit or illicit drug including heroin.
   - In 1999, methadone represented 3% of all deaths due to overdose/poisoning by medications and drugs; in 2008, methadone represented 33% of all deaths due to overdose/ poisoning by medications and drugs (both licit and illicit) in Oregon.
   - Methadone has unique pharmacological properties that increase the risk of adverse outcomes compared to other drugs used to treat chronic pain such as Percocet, OxyContin, Oxycodone, Hydromorphone and others. Methadone has a longer “half life” meaning that it takes longer for the medication to be eliminated from the bloodstream.
   - Individuals may accidentally or intentionally take more than the prescribed dose of methadone or take the medication more often than prescribed for a variety of reasons including confusion, forgetting the time of the last dose, inability to experience pain relief, or seeking a euphoric high from medications known to produce these effects.
   - Methadone is inexpensive compared to other opioid pain treatment options (an approximate 30 day cost of $8.10 compared to $360 for equianalgesic equivalent treatment with OxyContin).
   - Most deaths occur among Oregonians aged 35-54 age group.
   - Medical examiner records indicate that about 75% of methadone overdose decedents have a history of substance use disorder; about 50% had a history of mental illness.
   - Many deaths are occurring among persons prescribed methadone for pain treatment. Preliminary analysis of medical examiner data shows that about 40% of methadone overdose/poisoning decedents had evidence of being prescribed methadone. About an equal number had no evidence for a methadone prescription or authorized treatment.

3. Use of prescription opioid analgesics has increased in Oregon.
   - In 2007 Oregon was the 3rd largest per capita consumer of retail methadone (distributed from pharmacies) in the US (*US DOJ, Automation of Reports& Consolidated Orders System (ARCOS), 2007*).
   - Distribution of methadone (per capita) in Oregon increased over 2,000% between 1997 and 2006.
   - The increase in methadone distribution for retail (i.e. pharmacies) closely parallels the death rate associated with methadone overdose.
   - Oregon is among the states with the highest proportion of prescription painkiller misuse (National Survey on Drug Use and Health).

Unanswered questions:

1. What proportion of opioid deaths in Oregon is among Medicaid enrollees?

   Washington State found that 45% of opioid poisoning decedents were Medicaid enrollees, and that Medicaid enrollees were about six times more likely to die of opioid overdose compared to the non-Medicaid population. Research in Oregon should focus on determining whether a similar level of risk is present among the Medicaid population here.

2. Are Medicaid enrollees in Oregon disproportionately prescribed methadone?

   Methadone is inexpensive when compared to other prescription opioids. The low cost of methadone may increase incentives to prescribe the drug, possibly putting vulnerable populations at increased risk for opioid overdose/poisoning.

3. What proportion of deaths occurs among persons prescribed methadone (versus those using methadone, who don't have a prescription, i.e. diverted)?

   About 40% of methadone poisoning decedents were prescribed methadone, but do not know about decedents poisoned by other drugs.

4. What factors are associated with mortality among those under medical care for pain treatment (through pain specialty clinics, general practice, or other)?

History of substance use disorders among methadone poisoning decedents is high (among those prescribed methadone). Standard screening practices might reduce risk of death among those being treated for pain with prescription opioids.

5. What factors contribute to diversion of prescription painkillers?

   Data show that 60% of those who report misuse or nonmedical use of prescription pain relievers got those medicines from friends or family.

Next steps

Collect data on decedent risk factors by carrying out a study of opioid overdose decedents through the OHA Public Health Division.

Develop survey questions for the Behavioral Risk Factor Surveillance Survey to determine what factors influence drug sharing and what factors might decrease this practice among Oregonians.

II. Policy

Current state of knowledge:

- Policies might contribute to overdoses.
- Prescription benefit limits on chronic pain treatment may limit medications available (promotes use of methadone), may limit non-pharmacological options.
- Lack of adequate addiction and mental health treatment.

1. Policies already in place may help improve the situation.
   - Prescription Monitoring Program slated to start September 1, 2011 will provide prescribers access to information about patient drug use.
   - All prescribers of opiates are required to take continuing education in pain management (OR).
   - Federal Drug Administration (FDA) Risk Evaluation and Mitigation Strategies (REM) program will provide education and training to ensure

physicians prescribe opioids appropriately, and counsel their patients on safe use and disposal.

Unanswered questions:

1. How do policies affect:
   - Prescribing opioids for pain relief?
   - Counseling and monitoring?
   - Patients' misuse or abuse of drugs?
   - Sharing of pain pills with relatives or friends?
   - Doctor shopping to obtain multiple prescriptions?
   - Diversion of opioids leading to illicit sales, abuse and unintended deaths?
2. What are effective policies in place in other states?

Next steps:

1. Look at the policies created in Washington and Utah (and elsewhere).

2. Determine what balanced policy in Oregon would look like; consider what is already in place and what is in development.

III. Clinical Practice

Current knowledge:

1. What might contribute to opiate overdose?
   - Standardized prescribing guidelines for chronic pain are not widely adopted by prescribers.
   - Patients using opioids to manage chronic pain are not consistently screened for risk factors associated with substance use disorders using standardized risk assessment tools. Policy directives governing practice in this regard are generally applied at the individual clinic or provider network level, not a statewide policy level.
   - Healthcare providers lack understanding of addiction and therefore overlook signs of addiction.
   - When substance use disorders are recognized by healthcare providers or even patients, appropriate treatment for opioid addiction is hindered by

the stigma associated with using medication assisted treatments (methadone, Buprenorphine, Naltrexone) and the general lack of understanding of the benefits associated with medication assisted treatment. Medications other than methadone are fairly new and not widely understood by the medical community or even the addiction treatment community. However, there is a growing body of research about the substantial benefits related to using medications to treat addictions, particularly as related to opioid addiction.

- Clinicians are not informed when their patients enroll in a chemical dependency treatment programs.
- Clinicians are not informed when their patient overdoses.
- Cost limits treatment options for chronic pain patients.
  - Reliance upon methadone because it's inexpensive and preferred on drug formularies; and
  - Inability to provide Complementary Alternative Medicine (CAM) because it's not a covered benefit or due to cost if uninsured.
- Clinicians are not allowed to prescribe Buprenorphine without prior authorization.
- While many clinicians will treat their existing patients using Buprenorphine, they are reluctant to accept new patients with serious addiction histories.
- Patients expect and demand clinicians to prescribe opioids even if an opioid is not indicated.
- Patients and the public do not understand the risk of opioid misuse.
- Drug interactions increase risk of overdose and death. At highest risk are those prescribed methadone due to the cardiac and respiratory depression that occurs with methadone and the long half life of methadone.

2. What policies already in place may help improve the situation?
   - The Oregon Prescription Drug Monitoring Program.
   - Professional Board statements and recommendations.
   - Oregon Pain Commission policies.
   - Professional guidelines.

3. What questions do we still have unanswered?
   - What evidence is there for multidisciplinary treatments for chronic pain?
   - What populations are at risk for dying from opioids?

- What can prescribers do to reduce the risk of overdose and death?

4. What are our next steps?
   Prescriber education:
   - Improve prescriber continuing education about the use of opioids to treat acute pain, chronic pain, and addiction in every clinical discipline;
   - Improve professional addiction and pain treatment education;
   - Expand the capacity for physicians to receive continuing medical education hours related to this topic;
   - Include a minimum number of questions on certification examinations that relate to the topic of chronic pain management:
     - Include a minimum number of questions on certification examinations on addressing substance use disorders and use of medication assisted treatments particularly where opioids are concerned; and
     - Require specific information on prescription of methadone and patient medication management of methadone.
   - Disseminate standards of care for managing chronic pain;
   - Create and disseminate standards for prescribing opioids safely and effectively;
   - Standardize evaluation of safety and effectiveness of opioid therapy:
     - Track and document functional improvement and pain relief; and
     - Consider specialty consultation if there is evidence of adverse effects or lack of response.
   - When prescribing opioid therapy:
     - Assess patient to determine current or past alcohol or other substance abuse, including nicotine (Opioid Risk Tool, AUDIT, DAST, CAGE-AID);
     - Augment pharmacological care with behavioral therapies;
     - Assess depression severity and treat;
     - Document a baseline urine drug test with each patient;
     - Document a baseline assessment of function and pain;
     - Conduct a risk/benefit discussion with each patient;
     - Provide mandatory patient education that teaches self-management of chronic pain when initiating chronic opioid therapy; and
     - Document treatment goals that include improvements in function and pain and track and document patient progress or lack thereof.
   - After prescribing:

  - Routinely monitor patients for adverse effects and document treatment strategies and patient progress or lack thereof using standard measurements;
  - Routinely administer and document patient urine testing;
  - Conduct and document pill counts; and
  - Patient follow-up in treatment plan should include specify time intervals to monitor treatment.
- Safety:
  - Each patient should use a single prescriber or clinical practice;
  - Each patient should use a single pharmacy;
  - Prescribers should use the lowest effective dose;
  - Prescribers and patients should continuously assess for conditions that can potentiate opioid adverse effects, document those conditions and follow up on those conditions on a routine basis;
  - Prescribers should avoid prescribing opiates at the same time a patient is taking sedative-hypnotics, benzodiazepines, or barbiturates; and
  - Prescribers must monitor for medication misuse.
- Barriers:
  - There are a limited number of pain specialists and addictions medicine specialists;
  - Limited access to addiction treatment, behavioral therapy and mental health treatment. Roughly 25-40% of those individuals in need of these services access services annually according to estimates from national survey data and treatment episode data; and
  - Improve communication about opiate use and misuse between all care providers including primary care, emergency departments, alcohol and drug treatment providers, case workers, emergency medical services (EMS).
- Advocate for the increased availability of Buprenorphine:
  - Incentivize physicians to become Buprenorphine prescribers.
  - Encourage managed care companies to pay for Buprenorphine treatment.
  - Encourage managed care companies to remove prior authorizations requirements for Buprenorphine and other medications that demonstrate efficacy in treating opioid addiction.
- Create a feedback loop for prescribers so they can learn about their patients who experience negative consequences related to prescription drug misuse (legal issues, use of crisis or other emergency services);

- The medical examiner should notify the primary care provider of deceased when the death is caused by drug overdose;
- Chemical dependency treatment programs should notify patient primary care providers of their patient's entry into treatment for chemical dependency;
- Create patient education materials/website;
- Promote clinician use of the prescription drug monitoring program beginning in September 2011;
- Increase healthcare provider awareness of the efficacy of non-pharmacological treatments for pain;
- Educate the public about safe use and storage of opioids.

IV. Education

Current knowledge:

1. There are gaps in clinical education among prescribers:
   - Insufficient addiction and pain management education for health care payers, prescribers and medical students, patients, pharmacists, law makers, policy developers, and the general public.
   - Education for clinicians on the use of prescription methadone is not standardized nor is it evaluated.

2. Education policies already in place:
   - Mandatory continuing education in pain management (OR).
   - Screening, Brief Intervention and Referral to Treatment (SBIRT) for alcohol misuse and addition is incorporated into physician residency program at Oregon Health and Science University.

3. There is low public awareness of the dangers of opioid misuse and overdose.

Unanswered questions:

1. How do current clinical education policies and practices effect:
   - Clinician prescribing by specialty;
   - Counseling and monitoring patients using prescribed methadone for pain;
   - Patients' misuse or abuse of prescribed methadone for pain;

- Sharing of methadone with relatives or friends;
- Doctor shopping to obtain multiple prescriptions; and
- Diversion of opioids leading to illicit sales, abuse and unintended deaths.

Next steps for education:

1. Review the curriculum content, requirements, policies, and outcomes of clinical education in Washington and Utah (and elsewhere).

2. Assess the gaps in clinical education and determine appropriate standards and requirements needed to establish improved clinical education in Oregon for prescribers in each discipline that prescribe opiates for the relief of acute pain, the relief of chronic pain, and addiction.

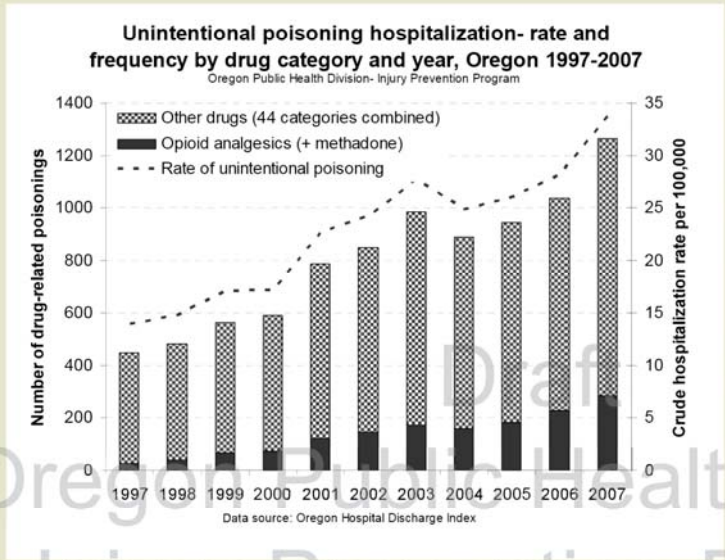
3. Study the needs and messaging content that would contribute to increased awareness and behavior change among Oregonians.

Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup
October 6, 2010

Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Hospitalizations for unintentional poisoning



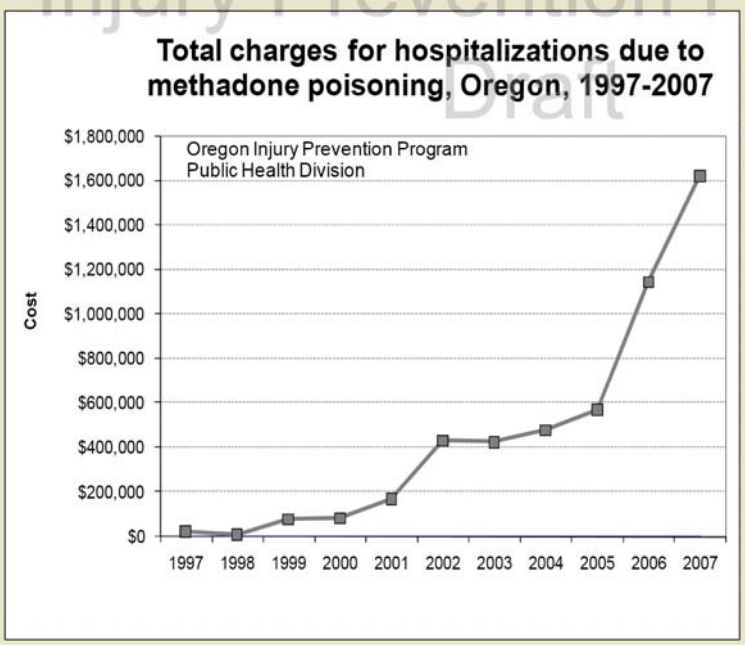
In 1997, opioid-related poisonings represented 5.6% of all medication and drug-related poisoning hospitalizations. In 2007, opioid-related poisonings represented 22.3% of all medication and drug-related hospitalizations in Oregon.

In 1997, methadone-related poisonings represented 0.7% of all medication and drug-related hospitalizations. In 2007, methadone-related poisonings represented 7.3% of all medication and drug-related hospitalizations in Oregon.

Hospitalization charges associated with methadone poisoning have increased 70-fold since 1997.

In 2007 Oregon was the 3rd largest per capita consumer of retail methadone (distributed from pharmacies) in the US. (*US Dept. of Justice, Automation of Reports and Consolidated Orders System (ARCOS), 2006*).

Draft
Oregon Public Health Division
Injury Prevention Program



Draft

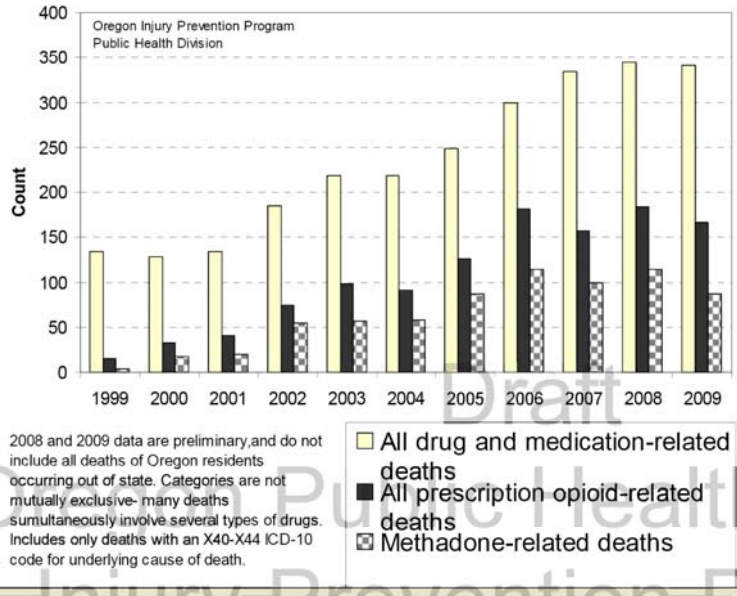
1

Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup
October 6, 2010

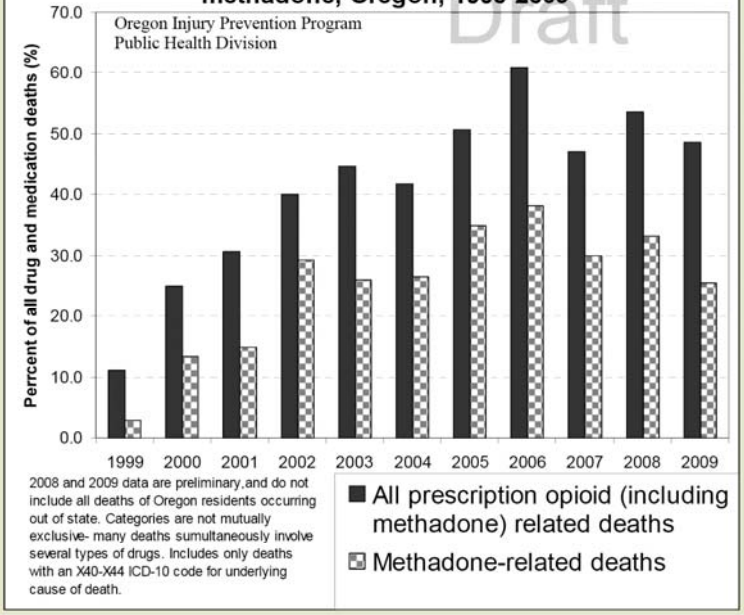
Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Number of deaths due to medications and illicit drugs, Oregon, 1999-2009



2008 and 2009 data are preliminary,and do not include all deaths of Oregon residents occurring out of state. Categories are not mutually exclusive- many deaths sumultaneously involve several types of drugs. Includes only deaths with an X40-X44 ICD-10 code for underlying cause of death.

Percent of medication and illicit drug-related deaths that involve prescription opioids and methadone, Oregon, 1999-2009



2008 and 2009 data are preliminary,and do not include all deaths of Oregon residents occurring out of state. Categories are not mutually exclusive- many deaths sumultaneously involve several types of drugs. Includes only deaths with an X40-X44 ICD-10 code for underlying cause of death.

Deaths-unintentional poisoning

In 1999, methadone represented 3% of all deaths due to poisoning by medications and drugs; in 2008, methadone represented 33% of all deaths due to poisoning by medications and drugs in Oregon.

In 1999, prescription opioids represented 11% of all deaths due to poisoning by medications and drugs; in 2008, prescription opioids represented 53% of all deaths due to poisoning by medications and drugs in Oregon.

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Injury Prevention Program
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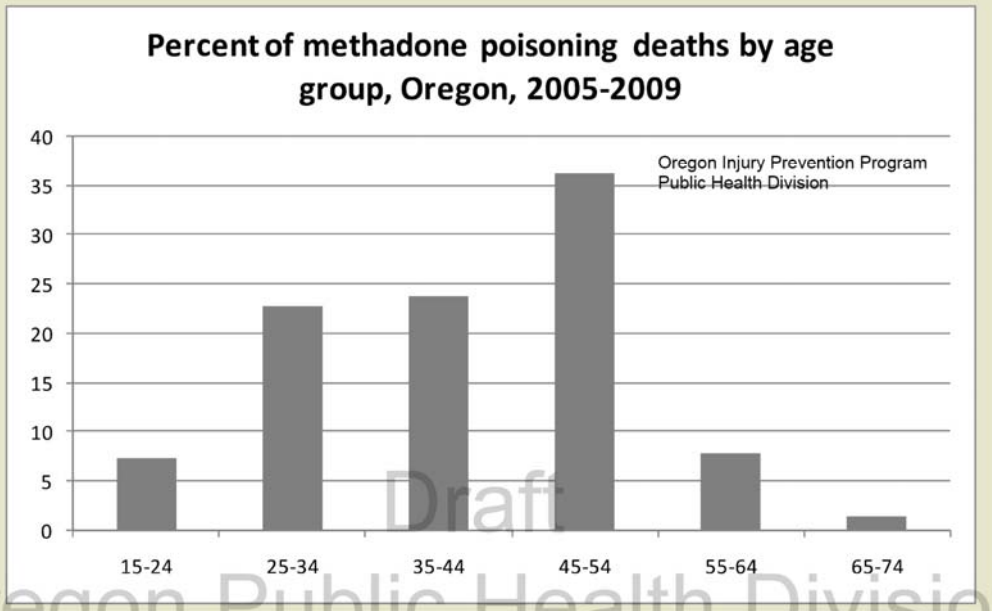
**2008-2009 mortality data are preliminary

Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup

Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Deaths-unintentional poisoning



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Injury Prevention Program
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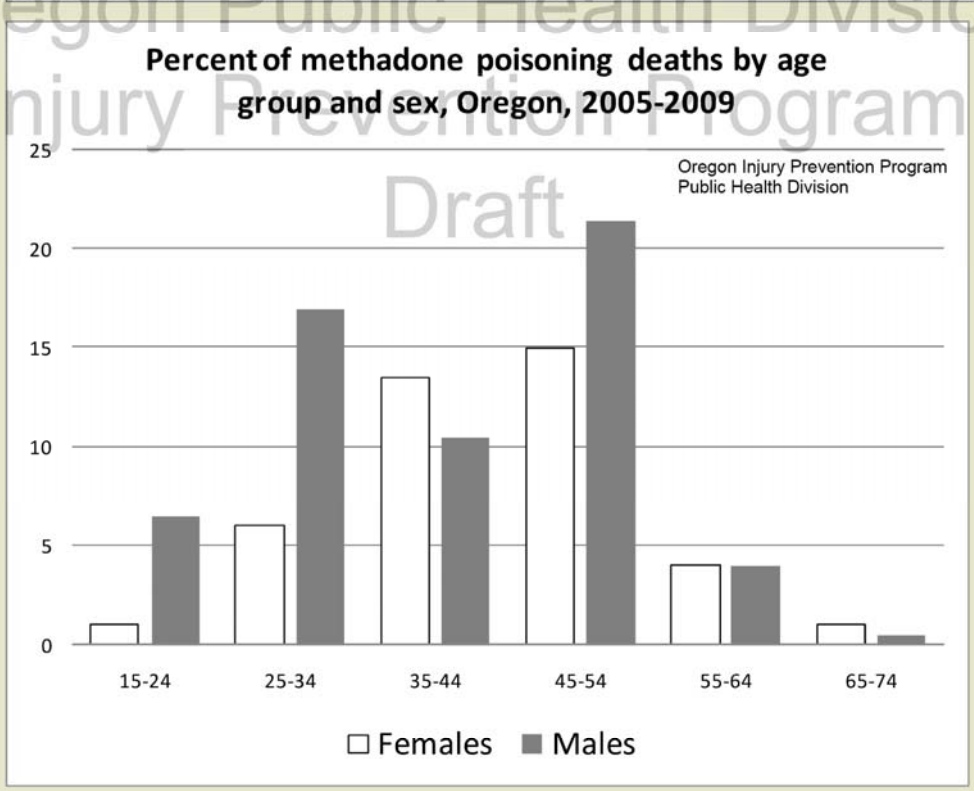

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Methadone Poisoning in Oregon

Data produced for the Oregon Prescription Opioid Poisoning Workgroup
October 6, 2010

Data: Oregon Public Health Division
Injury Prevention & Epidemiology Program
Contact: matthew.laidler@state.or.us

Deaths– medical examiner data

SAMPLE: 56 Decedents identified from ME records where methadone was listed as a cause of death and manner of death was not listed as intentional.

PRESCRIBED:

- 41% (23) had been prescribed methadone
- 30% (17) were not prescribed methadone
- For 29% (16), it was unknown whether methadone was prescribed or not

For those prescribed methadone (41%):

- 43% (10) had been prescribed the drug for pain treatment
- 26% (6) were prescribed for NTP/Methadone maintenance
- For 30% (7), it was unknown why they were prescribed methadone

OTHER DRUGS:

- 21% (12) had been prescribed other drugs (opioid or otherwise) in addition to methadone

ABUSE:

- For 77% (43) of decedents, abuse/misuse of methadone likely contributed to death (informants disclosed abuse, investigator stated abuse, patient was using more than prescribed dose, patient obtained same drug from multiple doctors, patient obtained drug from illicit source, multiple doses missing).
- For those prescribed methadone for pain, abuse likely contributed to death for 60% (6) of cases.

HISTORY OF ABUSE:

- For 75% (42) of decedents, there was a history of substance abuse mentioned in the report
- Among those prescribed methadone for pain, 60% (6) had a history of substance abuse

HISTORY OF TREATMENT

- 21% (12) of decedents had a history of addiction/substance abuse treatment
- 16% (9) had a history of methadone maintenance/NTP (including the 6 NTP/MM decedents)

MENTAL ILLNESS

- 52% (29) had mention of mental illness in the ME report

CHRONIC ILLNESS

- 25% (14) had mention of chronic illness in the ME report

HEROIN

- 25% (14) had a history of heroin use

POLYPHARMACY

- 29% (16) deaths involved polypharmacy with other Rx drugs; 18% (10) involved polypharmacy with illicit drugs; in total 46% (26) involved polypharmacy

EMPLOYMENT

- 39% (22) were unemployed
- 39% (22) were employed
- 11% (6) were students (college or HS)
- 11% (6) had unknown current employment status (missing data)

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Oregon Public Health Division
Injury Prevention Program
Draft

410-121-0040 Prior Authorization Required for Drugs and Products

(1) Prescribing practitioners are responsible for obtaining prior authorization (PA) for the drugs and categories of drugs requiring PA in this rule, using the procedures required in OAR 410-121-0060.

(2) All drugs and categories of drugs, including but not limited to those drugs and categories of drugs that require PA as described in this rule, are subject to the following requirements for coverage:

(a) Each drug must be prescribed for conditions funded by Oregon Health Plan (OHP) in a manner consistent with the Oregon Health Services Commission's Prioritized List of Health Services (OAR 410-141-0480 through 410-141-0520). If the medication is for a non-covered diagnosis, the medication shall not be covered unless there is a co-morbid condition for which coverage would be extended. The use of the medication must meet corresponding treatment guidelines, be included within the client's benefit package of covered services, and not otherwise excluded or limited;

(b) Each drug must also meet other criteria applicable to the drug or category of drug in these pharmacy provider rules, including PA requirements imposed in this rule.

(3) The Oregon Health Authority (Authority) may require PA for individual drugs and categories of drugs to ensure that the drugs prescribed are indicated for conditions funded by OHP and consistent with the Prioritized List of Health Services and its corresponding treatment guidelines (*see* OAR 410-141-0480). The drugs and categories of drugs that the Authority requires PA for this purpose are found in the OHP Fee-For-Service Pharmacy PA Criteria Guide (PA Criteria Guide) dated Jan. 1, 2011, incorporated in rule by reference and found on our Web page at:
http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html

(4) The Authority may require PA for individual drugs and categories of drugs to ensure medically appropriate use or to address potential client safety risk associated with the particular drug or category of drug, as recommended by the Pharmacy & Therapeutics Committee

(P&T) and adopted by the Authority in this rule (*see* OAR 410-121-0100 for a description of the DUR program). The drugs and categories of drugs for which the Authority requires PA for this purpose are found in the Pharmacy PA Criteria Guide.

(5) PA is required for all new drugs added to the National Drug Data File (NDDF):

(a) The new drug will be prioritized to be presented to the P & T Committee after the drug's NDDF add date. The P & T Committee will make additional drug specific recommendations to the Authority regarding PA criteria, if any, that should be adopted for the new drug:

(i) If the new drug is in a class where current PA criteria apply, all PA criteria associated with that class shall be required at the time the new drug is added to the NDDF;

(ii) If the new drug is indicated for a condition below the funding line on the Prioritized List of Health Services, PA shall be required to ensure that the drug is prescribed for a condition funded by OHP;

(b) PA for the new drug under section (5) of this rule remains in effect until such time as the Authority makes a determination regarding the applicability of PA criteria for the new drug or six months elapse from the drug's NDDF add date without a decision regarding PA criteria for that drug, whichever occurs first;

(c) Oral oncology medications, anti-retrovirals, and family planning drugs are excluded from the PA requirements in section (5) of this rule.

(6) PA is required for brand name drugs that have two or more generically equivalent products available and that are NOT determined Narrow Therapeutic Index drugs by the Oregon P&T Committee:

(a) Immunosuppressant drugs used in connection with an organ transplant must be evaluated for narrow therapeutic index within 180 days after United States patent expiration;

(b) Manufacturers of immunosuppressant drugs used in connection with an organ transplant must notify the department of patent expiration within 30 days of patent expiration for (5)(a) to apply;

(c) Criteria for approval are:

(A) If criteria established in subsection (3) or (4) of this rule applies, follow that criteria;

(B) If (6)(A) does not apply, the prescribing practitioner must document that the use of the generically equivalent drug is medically contraindicated, and provide evidence that either the drug has been used and has failed or that its use is contraindicated based on evidence-based peer reviewed literature that is appropriate to the client's medical condition.

(7) PA is required for non-preferred Preferred Drug List (PDL) products in a class evaluated for the PDL except in the following cases:

(a) The drug is a mental health drug as defined in OAR 410-121-0000;

(b) The original prescription is written prior to 1/1/10;

(c) The prescription is a refill for the treatment of seizures, cancer, HIV or AIDS; or

(d) The prescription is a refill of an immunosuppressant.

(8) PA may not be required:

(a) When the prescription ingredient cost plus the dispensing fee is less than the PA processing fees as determined by the Authority;

(b) For over-the-counter (OTC) covered drugs when prescribed for conditions covered under OHP or;

(c) If a drug is in a class not evaluated from the Practitioner-Managed Prescription Drug Plan under ORS 414.334.

Stat. Auth.: ORS Chap. 409.110, 413.042, 414.065, and 414.334

Stats. Implemented: 414.065

1-1-12

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Oral Anticoagulants Class Review – Addition of Warfarin

Month/Year of Review: January 2012
PDL Class: No current PDL class
Suggested Revision: Add warfarin to PDL
Current Status of Anticoagulants:
No PDL-status/no restrictions: warfarin
Non-preferred Oral Anticoagulants: rivaroxaban (pending) and dabigatran (pending)

FDA Approved Indications: Warfarin is approved for prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism; prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; and reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.[1]

Summary:
The vitamin K antagonist (VKA), warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy for Oregon Health Plan (OHP) patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population.

A meta-analysis for stroke prevention in patients with non-valvular AF found warfarin therapy to reduce stroke by 60%, which was 40% more efficacious than anti-platelet therapy.[2] The Cochrane Database for Systematic Reviews estimates that approximately 25 strokes and 12 disabling or fatal strokes would be prevented per year, for every 1000 primary prevention patients with AF treated with warfarin.[3]

Acute DVT treatment is an additional indication for anticoagulation. DVT is a serious medical condition that affects 1 in 1000 people and can lead to PE and related risk of morbidity and mortality.[4] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days and initiation of warfarin on the first treatment day.[5] Discontinuation of heparin preparations should occur when the INR reaches 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

For patients undergoing THR or TKR prophylactic anticoagulants are considered standard practice. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[6] The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (CHEST) on antithrombotic and thrombolytic therapy recommends treatment with warfarin, LMWH, or fondaparinux for 7 to 10 days for TKR and 10 to 35 days for THR.[7] Oregon Health Plan (OHP) fee-for-service FFS currently lists LMWHs, enoxaparin and dalteparin, as preferred, and fondaparinux (Arixtra®) and tinzaparin (Innohep®) as not preferred. Desirudin (Iprivask®) is not managed via PDL and currently has no utilization restrictions. In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims.

PDL Placement Recommendation:

Recommend maintaining warfarin as a preferred and first-line agent in the oral anticoagulant class for prophylaxis and treatment of thromboembolic disorders.

References:

1. Coumadin® Prescribing Information. Bristol-Myers Squibb, Inc. Princeton, NJ. January 2010.
2. Hart R, Pearce L, Aguilar M. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007;146:857-867.
3. Aguilar, M, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. The Cochrane Database of Syst Rev. 2009 (1): CD001927.
4. American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report, 2011. (Accessed October 27, 2011, at http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf.)
5. Hirsh J, Guyatt G, Albers G, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133;71S-109S.
6. American Academy of Orthopaedic Surgeons. Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty Evidence-Based Guideline and Evidence Report, 2011. (Accessed October 27, 2011, at http://www.aaos.org/research/guidelines/VTE/VTE_full_guideline.pdf.)
7. Hirsh J, Guyatt G, Albers G, et al. Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133;71S-109S.

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Month/Year of Review: January 2011
Generic Name: Dabigatran

End date of literature search: December 2011
Brand Name (Manufacturer): Pradaxa (Boehringer Ingelheim)
Dossier received: Yes
Comparator Therapies: Enoxaparin and warfarin

PDL Class: No current PDL class
Preferred Anticoagulants: enoxaparin and dalteparin
Non-preferred Anticoagulants: fondiparinux, tinzaparin, rivaroxaban (pending) and dabigatran (pending)
No PDL-status/no restrictions: warfarin

FDA Approved Indications: To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).

Summary:

- Dabigatran is a direct thrombin inhibitor used for oral stroke prophylaxis in patients with AF, as an alternative to vitamin K antagonists (VKA) such as warfarin. Dabigatran has few drug/food interactions and is not a substrate, inhibitor or inducer of CYP450 enzymes.[1]
- The recommended dabigatran dose is 150mg twice daily for AF. Dose adjustment to 75mg twice daily if CrCl 15-30 mL/min. No adjustments required with moderate hepatic dysfunction.

Efficacy and Safety Summary for FDA Approved Indications

Atrial Fibrillation

- Dabigatran approval was based on a large, prospective, non-blinded, randomized trial, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY).[2] RE-LY was a multi-center, multi-national, parallel group, non-inferiority trial comparing two blinded doses of dabigatran (110mg twice daily or 150 mg twice daily) with open-label warfarin with a target international normalized ratio (INR) range of 2-3. Mean time in therapeutic range (TTR) was 64%.[2]
- A high degree of bias is associated with an open-label study design. The FDA cited this concern in their review but felt that because there were significant differences shown in the double-blind comparison between the dabigatran doses, this helped to substantiate the results.[3] The rates of intracranial bleeds was the primary factor contributing to the composite outcomes.
- Two doses were studied in RE-LY, a 110 mg dose and a 150 mg dose. The 110mg dose was not approved and did not demonstrate superiority over warfarin. There was moderate-strength of evidence that dabigatran 150mg was superior to warfarin for the primary composite endpoint of stroke or systemic embolism (RR 0.65; 95% CI, 0.52 to 0.81; p<0.001, NNT 167). There was low-strength of evidence

that dabigatran 150mg had similar rates of all-cause mortality compared to warfarin. FDA analysis of RE-LY states that in patients whom INRs are well controlled, warfarin and dabigatran 150 mg twice daily carry the same risk of stroke or fatal events.[3]

- There was low-strength of evidence of similar rates of major bleeding with dabigatran 150mg, compared to warfarin, which was influenced by the TTR. There were significantly more gastrointestinal bleeds in the dabigatran 150mg group compared to warfarin. Dabigatran was associated with less intracranial bleeding, which was statistically significant and independent of TTR.[4]

Other Considerations:

- Dabigatran is associated with dyspepsia, which is the most commonly cited reason for drug discontinuation. In the dabigatran 150mg group annual discontinuation rates were 2% compared to 0.6% of warfarin patients.[2]
- An increased rate of myocardial infarctions (MI) were seen with both doses of dabigatran but neither were statistically significant after newly identified events were included in the revised data.[5]
- There is no antidote to reverse bleeding in a bleeding emergency. Unlike warfarin, vitamin K administration will not reduce the anticoagulant effects of dabigatran in the event of a major bleed.[1]
- The FDA has recently announced that they will be conducting a safety review of post-marketing reports of serious bleeding associated with dabigatran. At this time the FDA believes the benefits of dabigatran still exceed the risk.

Efficacy and Safety Summary on off-label Uses

Surgery Prophylaxis

- Three studies evaluated the use of dabigatran for prevention of VTE after TKR and THR. In TKR, the evidence found that dabigatran was noninferior to enoxaparin (European dosing regimen of 40mg daily was used compared to North American regimen of 30 mg twice daily) however, it was deemed inferior to enoxaparin when the North American dosing regimen was used. One fair quality study in THR showed dabigatran to be non-inferior to enoxaparin. All surgery prophylaxis studies included asymptomatic and symptomatic DVTs, in which the clinical utility of asymptomatic DVTs is unknown. Overall, the use of dabigatran for prophylaxis of DVT in patients undergoing THR and TKR has low level evidence to support its use.

Acute DVT Treatment

- There is one fair quality study of dabigatran use in the acute treatment of VTE (RECOVER), which demonstrated that dabigatran was noninferior to warfarin with similar rates of bleeding.

Cost Considerations:

Costs will be discussed in the executive session.

PDL Placement Recommendation:
There is low-moderate level of evidence to support the use of dabigatran in AF. The relative efficacy of dabiagatran compared to warfarin is still uncertain due to potential bias toward dabigatran as a result of an open-label study design. Sub-optimal INR control in the warfarin group in RE-LY suggests patients with well controlled INRs may not benefit from dabigatran treatment. It is recommended dabigatran be added to the PDL as a second line agent requiring prior authorization.

Data on using dabigatran for acute VTE is limited, however, due to limited oral anticoagulant options, dabigatran should be added to the PDL with a PA restriction for this indication as a second line option.

BACKGROUND/CURRENT LANDSCAPE
The vitamin K antagonist (VKA), warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy for Oregon Health Plan (OHP) patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population. A meta-analysis for stroke prevention in patients with non-valvular AF found warfarin therapy to reduce stroke by 60%, which was 40% more efficacious than anti-platelet therapy.[12] The Cochrane Database for Systematic Reviews estimates that approximately 25 strokes and 12 disabling or fatal strokes would be prevented per year, for every 1000 primary prevention patients with AF treated with warfarin.[13] However, there is a significant clinical need for an alternative to warfarin for treatment and prophylaxis of numerous conditions that require anticoagulation. Warfarin has a narrow therapeutic index, drug and dietary interactions, variable pharmacokinetics, and unpredictable pharmacodynamic responses, resulting in reduced protection against thromboembolic events and potentially causing serious bleeds.[14] Consequently, warfarin is often underutilized, with only 64% of eligible patients taking warfarin therapy.[15] Even with optimal management, some patients do not achieve adequate INR control.

Patients with AF are at a four to five-fold increased risk of stroke and systemic embolism compared to those without AF. Annual rates of stroke in patients with AF are estimated to be between 3-8%, depending on additional risk factors.[16] Anticoagulants are a key component to managing patients with AF that are at an increased risk of stroke from cardioembolic events. Stroke risk in AF patients is most commonly estimated using the $CHADS_2$ risk stratification scheme. This scheme estimates stroke risk based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack (Table 1).[17] The greater the number of risk factors present, the greater the risk of stroke. Current CHEST guidelines recommend anticoagulation for patients with AF and suggest aspirin therapy for patients with up to one risk factor and treatment with a VKA for patients with one or more risk factors or in secondary prevention patients.[18] The guidelines also recommend VKA therapy for patients with a $CHADS_2$ score of ≥2.

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[17]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Observed rates of venous thromboembolism(VTE) after total hip and knee replacement surgery occurs in approximately 5% of patients without recommended prophylactic anticoagulation. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[19] The CHEST guidelines recommend at least 10 days of therapy and up to 35 days with either warfarin, low molecular weight heparin (LMWH), or fondaparinux for knee and hip replacement.[18] OHP covers all LMWH products, fondaparinux (Arixtra®) and desirudin (Iprivask®). In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims.

VTE is a serious medical condition that can lead to pulmonary embolism and related risk of morbidity and mortality.[20] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days and initiation of warfarin on the first treatment day.[18] Discontinuation of heparin preparations should occur when the INR reaches 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

CLINICAL PHARMACOLOGY

Dabigatran is a competitive, direct thrombin inhibitor with active metabolites (acyl glucuronides). Dabigatran inhibits free and clot-bound thrombin, as well as thrombin-induced platelet aggregation. During the common pathway of the coagulation cascade, thrombin is required for the conversion of fibrinogen to fibrin which is then cross-linked to form a thrombus. Inhibition of this transformation prevents the development of thrombi.[1]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:	All-cause Mortality
	Major bleeding
DVT:	Symptomatic DVT
DVT Prophylaxis:	PE
	Symptomatic DVT
AF:	Stroke

Study Endpoints:

RE-LY: Stroke or Systemic Embolism

RECOVER: VTE and Related death

REMOBILIZE, REMODEL, RENOVATE: Total VTE and All-cause mortality

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
RE-LY[2,5]									
Connolly SJ, et al Phase III, RCT, PG	1. Dabigatran 110mg bid 2. Dabigatran 150mg bid 3. Warfarin adjusted to INR of 2-3	Age: 71 yrs Male: 64% Prior stroke/TIA: 20% $CHADS_2$: 2 Avg. TTR (warfarin): 64%	1. 6015 2. 6076 3. 6022	Median F/U 24 months	<u>Stroke or Systemic Embolism:</u> D 110mg: 182 (1.54%) W: 199 (1.71%) RR 0.90 95% CI 0.74 to 1.10, p<0.001 fo noninferiority P= 0.30 for superiority D 150mg: 134 (1.11%) W: 199 (1.71%) RR 0.65 95% CI 0.52-0.81, p<0.001 for superiority <u>Stroke:</u> D 110mg: 171 (1.44%) W: 185 (1.57%) RR .92 95% CI 0.74 to 1.13 P=0.41 D 150mg: 122 (1.01%)	NS ARR 0.60% NNT 167 NS ARR 0.56%	<u>Major Bleeds:</u> D 110mg: 2.87% RR 0.80 95% CI 0.70 to 0.93 p=0.003 D 150mg: 3.32% RR 0.93 95% CI 0.81 to 1.07 p=0.32 W: 3.57%	ARR 0.7% NNH 142 NS	• Fair • Open-label design may bias results in favor of dabigatran • TTR for warfarin patients wa 64% suggesting suboptimal warfarin use. • Major bleeds were less in dabigatran groups only in centers where TTRs were worse than median. • INR testing protocol was not clearly outlined. TTR has a direct effect on safety and efficacy. • Use in a broader patient population is needed to define MI risk, GI bleeding and effect of no antidote.

					W: 185 (1.57%) RR 0.64 95% CI 0.51 to 0.81 P<0.001 <u>All Cause Mortality:</u> D 110mg: 446 (3.75%) W: 487 (4.13%) RR 0.91 95% CI 0.80 to 1.03 P=0.13 D 150mg: 438 (3.64%) W: 487 (4.13%) RR 0.88 95% CI 0.77 to 1.00 P=0.051	NNT 179 NS NS			
RE-COVER[11]									
Schulman S, et al Phase III, RCT, DB, PG	1. Dabigatran 150mg bid 2. Warfarin adjusted to INR of 2-3 .	Age: 54 yrs Male: 58% Avg. TTR (warfarin): 60% <u>Inclusion:</u> Patients 18 or older with acute, symptomatic, objectively verifie proximal DVT of the legs or pulmonary embolism whom 6 mo. of anti-coagulation was deemed appropriate. <u>Exclusion:</u> Symptoms >14 days, PE with	1. 1273 2. 1266	Median F/U 5.5 months tx with 1 month F/U	<u>VTE or Related death:</u> D 150mg: 30 (2.4%) W: 27 (2.1%) HR 1.10 95% CI -0.65 to 1.84 p<0.001 <u>Symptomatic DVT:</u> D 150mg: 16 (1.3%) W: 18 (1.4%) HR 0.87 95% CI 0.44 to 1.71 <u>All Cause Mortality:</u> D 150mg: 21 (1.6%) W: 21 (1.7%) HR 0.98 95% CI 0.53 to 1.79	ARR 0.4% NNT 250	<u>Major Bleeding:</u> D 150mg: 20 (1.6%) W: 24 (1.9%) HR 0.82 95% CI 0.45 to 1.48 p=0.38	NS	• Fair • No protocol was given for INR testing. TTR for warfarin patients could influence efficacy and safety results • TTR for warfarin patients wa 60%.

		hemodynamic instability or requiring thrombolytics, additional warfari indication, high risk of bleeding, unstable CV disease, and renal and liver abnormalities							
RE-MOBILIZE[6]									
Ginsberg JS, et al Phase III, RCT, DB, PG	1. Dabigatran 220mg QD 2. Dabigatran 150mg QD 3. Enoxaparin 30mg BID (North American suggested dosing)	Age: 66 yrs Male: 43% Time to first dose: 9.5 hrs First dose of dabigatran. was ½ assigned dose <u>Inclusion:</u> Patients 18 and over undergoing primary elective unilateral knee arthroplasty <u>Exclusion:</u> Bleeding disorder uncontrolled htn, surgery, condition or medication predisposing pt. to bleeding, abnormal liver fxn renal insufficiency	1. 604 2. 649 3. 643	Median tx duration : 14 days F/U: 3 mo	<u>Total VTE + all-cause mortality:</u> D 220mg: 188 (31.1%) E: 163 (25.3%) RR 1.2 95% CI 1.0 to 1.5 D 150mg: 219 (33.7%) E: 163 (25.3%) RR 1.33 95% CI 1.1 to 1.6 <u>Nonfatal PE:</u> D 220mg: 6 (1.0%) E: 5 (0.8%) RR 1.3 95% CI 0.40 to 4.2 D 150mg: 0 (0%) E: 5 (0.8%)	NA NA NA	<u>Major Bleeding:</u> D 220mg: 5 (0.6%) E: 12 (1.4%) RR 0.42 95% CI 0.15 to 1.2 D 150mg: 5 (0.6%) E: 12 (1.4%) RR 0.42 95% CI 0.15 to 1.2		• Fair • Dabigatran deemed inferior due to exceeding non-inferiority margin • High number of patients (26 30%) excluded from analysis • Primary outcome was a composite endpoint including symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVT is unknown • No protocol given for VTE diagnosis • Concomitant use of ASA and selective cox-2 inhibitors allowed • Compression stockings allowed • Bilateral venography
RE-MODEL [7]									
Eriksson BI, et al	1. Dabigatran 220mg QD	Age: 68 yrs Male: 45% Time to first	1. 503	Median Tx duration: 8 days	<u>Total VTE + all-cause mortality:</u> D 220mg: 183 (36.4%)		<u>Major Bleeding:</u> D 220mg: 9 (1.5%) E: 9 (1.3%)		• Fair • Primary endpoint including

Phase III, RCT, DB, PG	2. Dabigatran 150mg QD 3. Enoxaparin 40mg QD (European suggested dosing for TKR)	dose: 3.5 hrs First dose of dabigatran was ½ assigned dose Inclusion: Patients 18 and older undergoing unilateral TKR Exclusion: Same as above	2. 526 3. 512		E: 193 (37.7%) RR 0.97 95% CI 0.82 to 1.1 D 150mg: 213 (40.5%) E: 193 (37.7%) RR 1.1 95% CI -0.23 to 0.1 Nonfatal PE: D 220mg: 0 (0%) E: 1 (0.1%) D 150mg: 1 (0.1%) E: 1 (0.1%) RR 0.98 95% CI 0.06 to 15.7 Symptomatic DVT: D 220mg: 1 (0.1%) E: 8 (1.2%) RR 1.0 95% CI 0.06 to 16 D 150mg: 1 (0.1%) E: 8 (1.2%) RR 0.37 95% CI 0.1 to 1.4		RR 1.1 95% CI 0.46 to 2.8 D 150mg: 9 (1.3%) E: 9 (1.3%) RR 0.99 95% CI 0.40 to 2.5		symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVTs is unknown • Excluded 25% of patients in primary outcome analysis • No protocol given for VTE diagnosis • Unclear if central adjudicators were blinded • Dosing regimen for enoxaparin is common in Europe for joint replacement but not in North America.
RE-NOVATE [8]									
Eriksson BI, et al Phase III, RCT, DB, PG	1. Dabigatran 220mg QD 2. Dabigatran 150mg QD 3. Enoxaparin 40mg QD	Age: 64 yrs Male: 44% Inclusion: Patients 18 and older undergoing unilateral THR Exclusion: Same as above	1. 880 2. 874 3. 897	Median Tx duration: 33 days Median f/u: 94 days	Total VTE + all-cause mortality : D 220mg: 53 (6.0%) E: 60 (6.7%) RR 0.90 95% CI 0.63 to 1.3 D150mg: 75 (8.6%) E: 60 (6.7%) RR 1.3 95% CI 0.93 to 1.8	NA	Major Bleeding: D 220mg: 23 (2.0%) E: 18 (1.6%) RR 1.3 95% CI 0.74 to 2.4 D 150mg: 15 (1.3%) E: 18 (1.6%) RR 0.83 95% CI 0.42 to 1.6		• Fair • Primary endpoint including symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVTs is unknown • Excluded 23% of patients in primary outcome analysis (mITT) • No protocol given for VTE diagnosis

					PE: D 220mg: 5 (0.4%) E: 3 (0.3%) RR 1.7 95% CI 0.40 to 7.0 D 150mg: 1 (0.1%) E: 3 (0.3%) RR 0.33 95% CI 0.03 to 3.2 Symptomatic DVT: D 220mg: 6 (0.5%) E: 1 (0.1%) RR 6.0 95% CI 0.73 to 50 D 150mg: 9 (0.8%) E: 1 (0.1%) RR 8.90 95% CI 1.1 to 70				• Dosing regimen for enoxaparin is common in Europe for joint replacement

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range

Study Details –

FDA approval of dabigatran was based on a phase III trial in 18,113 patients with AF, the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY).[2,5] RE-LY was a multi-center, multi-national, prospective, randomized, parallel group, non-inferiority trial comparing two blinded doses of dabigatran (110mg twice daily or 150 mg twice daily) with open-label warfarin with a target INR range of 2-3. Patients had at least one $CHADS_2$ risk factor. Median follow-up was two years and the primary endpoint of the trial was time to first occurrence of stroke (ischemic or hemorrhagic) or systemic embolic event (SEE). The primary safety outcome measure was major bleeding. Patients had similar baseline characteristics, with a mean age of 71, an average $CHADS_2$ score of 2.1 and 64% were male. Over half of the enrolled patients had been on previous long-term VKA therapy and the other half were treatment naïve to VKA.

There was low-strength of evidence from the RELY trial that dabigatran 110mg was non-inferior to warfarin for the primary endpoint of stroke or systemic embolism. There was also low-strength of evidence for dabigatran 110mg that incidence of stroke and all-cause mortality rates were similar to warfarin (RR 0.91; 95% CI, 0.80 to 1.03; p=0.13) with low-strength of evidence of reduced rates of major bleeding. There was low-strength of evidence that dabigatran 150mg was superior to warfarin for the primary endpoint of stroke or systemic embolism (RR 0.65; 95% CI, 0.52 to 0.81; p<0.001) and for the component outcome of stroke, with a NNT of 167 and 179, respectively. There was low-strength of evidence that dabigatran 150mg had similar rates of all-cause mortality compared to warfarin and no difference in major bleeding rates.

RELY was subject to a high risk of bias based on open-label warfarin arm as a comparator. The FDA cited this concern in their review but felt that because there was significant differences shown in the double-blind comparison between the dabigatran doses that this helped to substantiate the results.[3]

FDA analysis of RE-LY states that in patients whom INRs are well controlled, warfarin and dabigatran 150 mg twice daily carry the same risk of stroke or fatal events.[3] Additionally, the FDA associated the benefits in all-cause mortality rates in favor of dabigatran was driven by centers where TTR was worse than the median. The incidence of major bleeds and gastrointestinal bleeding decreased in the warfarin groups as TTR improved and major bleeds were less in dabigatran groups only at centers in which TTR was worse than the median. However, rates of intracranial bleeds were not affected by TTR, with consistently lower incidences in both dabigatran groups.[4] Intracranial bleeds were also the major contributor of the primary composite outcome.

Off-label Indications

Acute VTE Treatment

In RECOVER a non-inferiority study of dabigatran compared to warfarin for the acute treatment of VTE was done in over 2500 patients. Participants were randomly assigned in a blinded manner to dabigatran 150mg twice daily or warfarin, dose-adjusted to an INR of 2.0-3.0, after

initial treatment with parenteral anticoagulation (median duration of 9 days).[11] The primary outcome measure was the 6-month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths. Noninferiority was determined for the hazard ratio with the predefined margin of 2.75 and the difference in risk with the predefined margin of 3.6 percentage points.

RECOVER had moderate-strength of evidence that dabigatran is noninferior to warfarin for the primary endpoint of VTE or related death. Additionally, there was moderate-strength of evidence that major bleeding rates were similar for dabigatran and warfarin.

The RE-COVER study showed dabigatran to be as effective as warfarin over a six month time period for acute treatment of VTE. Warfarin treated patients were noted to be in the therapeutic range only 60% of the time, which could overestimate the effectiveness of dabigatran in comparison. A statistically significant number of patients discontinued treatment in the dabigatran group compared to warfarin, suggesting clinically relevant issues with tolerability with long term use.

VTE Prevention

Dabigatran was studied for prevention of VTE after TKR in 5,266 patients in the RE-MOBILIZE and REMODEL studies.[6,7] In the RE-MOBILIZE study patients received either dabigatran 220mg or dabigatran 150mg once daily or enoxaparin 30mg twice daily (North American dosing regimen) in a randomized, double blind fashion for a mean treatment duration of 14 days. In the REMODEL study patients received dabigatran 150mg, dabigatran 220mg once daily or enoxaparin 40mg subcutaneous once daily (European dosing regimen) in a randomized, double blind design for a median treatment of 8 days. The primary efficacy outcome was the composite of total VTE events (symptomatic or venographic) and all-cause mortality.

The two studies had conflicting primary endpoint results, with RE-MOBILIZE having low-strength of evidence that dabigatran 220mg and 150mg doses were inferior to enoxaparin in the prevention of VTE after TKR. In the REMODEL study there was low-strength of evidence that showed both doses of dabigatran were non-inferior to enoxaparin. In respect to component endpoints, there was low-strength of evidence that enoxaparin had less distal DVTs. Major bleeding rates were low in both studies, with slightly higher rates with enoxaparin in REMOBILIZE and equal or less major bleeding with enoxaparin than dabigatran in the REMODEL study.

RE-NOVATE evaluated the efficacy of dabigatran for the prevention of VTE in patients undergoing THR compared to enoxaparin.[8] Patients received dabigatran 150mg, dabigatran 220mg once daily or enoxaparin 40mg subcutaneous once daily in a randomized, double blind design for a median duration of 33 days. The primary efficacy outcomes was the composite of total venous thromboembolism (venographic or symptomatic) and mortality from all causes.

There was low-strength of evidence that dabigatran was noninferior to enoxaparin for the primary outcome measure in THR. There was also low-strength of evidence of reduced VTE related mortality with dabigatran 220mg compared to enoxaparin, although not statistically significant. Data for major bleeding rates demonstrated a moderate-strength of evidence that dabigatran 220mg was associated with more major bleeding than enoxaparin and dabigatran 150mg was associated with less major bleeding.

High numbers of patients were excluded because of the inability to adequately assess thromboembolism by contrast venography. The primary outcome was a composite measurement of symptomatic and venographic data, in which asymptomatic DVTs accounted for the majority of the events. The clinical importance of asymptomatic DVTs has yet to be determined and a bias in detecting events may have been present to do unilateral instead of bilateral venography. Canadian Agency for Drugs and Technologies in Health (CADTH) preformed a systematic review and found no statistically significant differences between dabigatran and enoxaparin in the safety and efficacy endpoints when used for TKR and THR prophylaxis.[9] The Cochrane Database for Systematic Reviews also evaluated direct thrombin inhibitors (DTI) for the prevention of VTE following TKR and THR. They concluded that no difference was found when only symptomatic VTE events were compared between groups. They caution, that the occurrence rate of symptomatic VTEs are so low, that none of the studies enrolled enough participants for them to be powered appropriately to make this determination.[10] A sensitivity analysis on the timing of anticoagulation initiation was also performed, based on evidence that this variable may impact the effectiveness of therapy as much as the actual treatment itself. The analysis found that direct thrombin inhibitor treatment started before surgery, resulted in less VTEs than treatment started after surgery, in comparison with LMWH. The Cochrane report concludes that DTIs are considered equally effective to LMWH in the prevention of VTEs in patients undergoing TKR and THR, but, overall there is insufficient evidence to support the use of dabigatran in preference to LMWH.[10] The American Academy of Orthopedic Surgeons Guideline on Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty analyzed data on pharmacologic agents, including dabigatran, for the prevention of VTE and found no difference between treatments in regards to efficacy or safety.[19]

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

Active pathological bleeding and history of serious hypersensitivity reaction are contraindications to dabigatran therapy.[1]

Bleeding: Like all anticoagulants, dabigatran increases the risk of bleeding and can cause significant or even fatal bleeding in certain patients. The risk for bleeding increases with dose and when other drugs that also increase the risk of bleeding are used concurrently. These include anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of non-steroidal anti-inflammatory medications.[1,2]

Overall, the rate of major bleeding was comparable to active controls in the studies except for a lower rate for dabigatran 110mg in RE-LY. In the RE-LY trial, there was a lower rate of life-threatening bleeds, especially intracranial bleeds with the dabigatran group compared to warfarin, while rates of GI bleeds were more common with dabigatran. When patient's INR is within range >65.5% of the time, rates of major bleeds are higher with dabigatran 150mg treatment.[2] Also, in patient's >80 years of age, dabigatran 150 mg was associated with significantly more major bleeding events compared to warfarin.[2]

Myocardial Infarction: A higher number of myocardial infarctions were seen in the dabigatran groups compared to warfarin in the RE-LY trial.[2] According to the FDA's review of the data, the reason for the excess events is unclear and cannot be adequately explained by baseline characteristics or concomitant treatments.[3] Rates were not dose-dependent and could be more significant in a broader population.

Tolerability (Drop-out rates, management strategies):

Gastrointestinal events were the most frequently cited adverse event resulting in treatment discontinuation. The risk of dyspepsia with dabigatran therapy was highest within the first few weeks of treatment. Annual treatment discontinuation rates due to dyspepsia were higher with dabigatran compared to warfarin, 2% vs. 0.6%, respectively.[2] Overall dropout rates due to adverse events were also higher with dabigatran 150mg (21%) compared to warfarin (16%).[2]

Pregnancy/Lactation rating:
Dabigatran is Pregnancy Category C and has been shown to decrease the number of implantations and increase the number of dead offspring when used in female rats.[1,3] It is not known if dabigatran is excreted in human milk.[1]

Unanswered safety questions:
Revised data showed a higher incidence of MI in both dabigatran groups compared to warfarin but they were not statistically significant.[5] Cardiovascular effects will need to be followed as dabigatran is used in the general population to ensure there is no increased risk. Unlike warfarin, vitamin K administration will not reduce the anticoagulant effects of dabigatran in the event of a major bleed. While there is no antidote to dabigatran, administration of fresh frozen plasma, red blood cells, or dialysis are unproven options to reduce hemorrhagic complications.[1] Other questions include the safety of using tissue plasminogen activator in patients taking dabigatran.

Dose Index (efficacy/toxic):
For patients with a creatinine clearance (CrCl) >30 mL/min, the recommended dose of dabigatran is 150 mg twice daily without regards to meals. For patients with CrCl between 15-30mL/min, the recommended dose of dabigatran in 75 mg orally twice daily.[1] Use of dabigatran in patients with a CrCl <15 mL/min or on dialysis is not recommended[1]. In patients with moderate renal impairment(CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole would produce dabigatran concentrations similar to those with severe renal impairment. The manufacturer recommends reducing the dose to dabigatran 75mg twice daily.[1] It is not recommended to use dabigatran and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30mL/min). Dabigatran concentrations increase with severity of renal impairment, based on pharmacokinetic modeling.[21] No dose adjustment is necessary for patients with mild hepatic dysfunction.
Capsules must be swallowed whole. Chewing, crushing, breaking, or emptying the contents of the capsule can result in up to a 75% increase in oral bioavailability[1]. Once opened, the product should be used within 4 months and kept in its original bottle.[21] If a dose is missed, it should be taken as soon as possible, unless it is within six hours of the next scheduled dose, then the dose should be skipped.[1]

Initially, liver function tests were performed monthly, due to hepatoxicity related to another direct thrombin inhibitor, ximelagatran. At six months the safety monitoring board deemed this frequency of testing to be unnecessary as dabigatran therapy resulted in similar liver function test elevations as warfarin, 1.9% vs. 2.2%, respectively.[2]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for dabigatran (generic)	None	None	None	None	Dalteparin
LA/SA for Pradaxa (brand)	None	None	None	None	Plavix Paclitaxel

					Procardia XL Prenexa

Common Drug-Related Adverse Events *[2]			
Adverse Events (1) **(MedDRA System Organ Class and Preferred Term)**	**Dabigatran 110 mg bid** **n (%)**	**Dabigatran 150 mg bid** **n (%)**	**Warfarin** **n (%)**
Number of Patients	**n=6015**	**n= 6076**	**n=6022**
Cardiac Disorders			
Chest Pain	312 (5.2)	377 (6.2)	357 (5.9)
Atrial Fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Gastrointestinal Disorders			
Diarrhea	330 (5.5)	357 (5.9)	349 (5.8)
Dyspepsia	707 (11.8)	688 (11.3)	348 (5.8)
Respiratory Disorders			
Cough	344 (5.7)	348 (5.7)	364 (6.0)
Dyspnea	557 (9.3)	580 (9.5)	586 (9.7)
Musculoskeletal Disorders			
Arthralgia	270 (4.5)	335 (5.5)	346 (5.7)
Back Pain	316 (5.3)	314 (5.2)	337 (5.6)
Nervous System Disorders			
Headache	457 (7.6)	458 (7.6)	554 (9.2)
Dizziness	486 (8.1)	506 (8.3)	568 (9.4)
Vascular Disorders			
Peripheral Edema	473 (7.9)	478 (7.9)	468 (7.8)
Other			
Fatigue	399 (6.6)	401 (6.6)	372 (6.2)
Nasopharyngitis	337 (5.6)	330 (5.4)	336 (5.6)

* Adverse events occurring in more than 5% of patients in dabigatran treatment groups.

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Dabigatran 150 mg	Capsule	Oral	Twice daily	CrCl 15-30mg/mL use elderly dosing	No change seen in moderate hepatic dysfunction	N/A	75mg twice daily*	May be taken with or without food Dabigatran 110mg dosage form used in studies is not available

* The 75 mg twice daily dose has not been studied. Concerns over dabigatran accumulation in patients with normal renal function have been raised. Patients with renal impairment may have a higher risk of drug accumulation and subsequent bleeding.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	3-7%*
Protein Binding	35%
Elimination	7% urine, 86% feces
Half-Life	12-17 hours
Metabolism	Conjugation to acyl glucuronides

* Do not crush capsules, bioavailability increases 75%.

ALLERGIES/INTERACTIONS

Drug-Drug:

Concomitant use of dabigatran with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should be avoided.[1] P-gp inhibition and impaired renal function are the most important risk factors that may cause increases in dabigatran concentrations[1] In clinical studies exploring the impact of dabigatran on other drug therapies, dabigatran did not meaningfully impact the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.[1] In patients with moderate renal impairment, concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole would produce dabigatran concentrations similar to those with severe renal impairment. The manufacturer recommends reducing the dose to dabigatran 75mg twice daily.[21]

Food-Drug:

No food-drug interactions have been reported.[1]

Allergy/Cross Reactive Substances:

In the RE-LY trial, drug hypersensitivity was reported in <0.1% of patients. No cross-sensitivities have been reported.[1]

APPENDIX:

Oral Direct Thrombin Inhibitors

Goal(s):

- Promote safe and effective therapies for oral direct thrombin inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes:** Go to #2	**No:** Go to #4
2. Will the prescriber consider a change to warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #3
3. Is the patient unable to take preferred oral anticoagulant,warfarin, due to one of the following: - unstable INR - warfarin allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for 1 yr.	**No:** Deny. Recommend warfarin trial.
4. Does the patient have a diagnosis requiring acute or recurrent DVT treatment?	**Yes**: Go to #5	**No:** Deny (Medical Appropriateness)
5. Will the prescriber consider a change to a preferred anticoagulant?	**Yes:** Additional information can be found at:	**No:** Go to #6

	http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	
6. Is the patient unable to tolerate preferred anticoagulants due to one of the following: - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred anticoagulants.

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Month/Year of Review: January 2012
End date of literature search: November 2011
Generic Name: Rivaroxaban
Brand Name (Manufacturer): Xarelto (Janssen Pharmaceuticals)
PDL Class: No current PDL class
Comparator Therapies: Enoxaparin and warfarin
Preferred Anticoagulants: enoxaparin and dalteparin
Non-preferred Anticoagulants: fondiparinux, tinzaparin, rivaroxaban (pending) and dabigatran (pending)
No PDL-status/no restrictions: warfarin

FDA Approved Indications: Rivaroxaban is indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing total knee replacement (TKR) or total hip replacement (THR) surgery. Rivaroxaban is also approved to reduce the risk of stroke in patients with non-valvular atrial fibrillation (AF).

Dossier received: Yes

Summary:

- Rivaroxaban is the first oral factor Xa inhibitor. Rivaroxaban differs from warfarin with respect to minimal food and drug interactions, absence of routine laboratory monitoring and quick onset of acton.[1]

Prophylaxis of DVT

- Rivaroxaban is dosed for prophylaxis of DVT as 10mg once daily without regard to food. Use cautiously in moderate renal impairment (CrCl 30-50 ml/min). Do not use in severe renal impairment (CrCl <30 ml/min) due to increased rivaroxaban exposure and pharmacodynamic effects in these patients. Monitor patients with moderate renal impairment (CrCl 30 to 50 mL/min) for signs or symptoms of bleeding. Avoid use in moderate or severe hepatic impairment or in hepatic disease with coagulopathy.

Nonvalvular Atrial Fibrillation

- Rivaroxaban is approved for atrial fibrillation, given as 20mg daily with the evening meal, for patients with CrCl >50 mL/min. For patients with CrCl of 15 to 50 mL/min a dose of 15 mg with the evening meal is recommended. Rivaroxaban is not recommended for a CrCL of <15 mL/min.

Efficacy and Safety Summary on FDA Approved Indications

Surgery Prophylaxis

- Rivaroxaban approval for patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery was based on three large, prospective, randomized, double blind, double dummy trials.[2,3,4] RECORD 2 and 4 are included in the evidence table, however, they were deemed poor studies based on FDA summaries on the quality of data.
- There was low-strength of evidence from RECORD 1 and 3 that rivaroxaban was similar to enoxaparin in regards to the component outcomes of all-cause mortality, symptomatic venous thromboembolism (VTE) and non-fatal pulmonary embolism. However, the use of the European enoxaparin dosing regimen of 40mg once daily in RECORD 3, limits the applicability of the results to patients in the United States were the recommended dosing regimen for DVT prophylaxis in patients undergoing TKR is 30mg twice daily.
- There was low-strength of evidence to suggest major bleeding rates were slightly higher for rivaroxaban compared to enoxaparin in both RECORD 1 and 3 studies, although not statistically significant.

Atrial Fibrillation

- ROCKET AF was a phase III, DB, DD, RCT in over 14,000 patients in 45 countries with nonvalvular atrial fibrillation who were at moderate to high risk of stroke. Patients were randomly assigned to rivaroxaban 20mg daily or dose-adjusted warfarin (INR 2.0-3.0). The primary efficacy analysis was the composite of stroke (ischemic and hemorrhagic) and systemic embolism.[6]
- There was low-strength of evidence from ROC KET AF that rivaroxaban was noninferior to warfarin for the composite outcome of stroke and systemic embolism (HR 0.88; 95% CI, 0.75 to 1.03; p<0.001 for noninferiority, p=0.12 for superiority). There was low-strength of evidence that major bleeding rates were similar between rivaroxaban and warfarin (HR 1.04; 95% CI, 0.90 to 1.20, p=0.58).
- Concerns over suboptimal warfarin use in ROCKET AF makes conclusions on relative efficacy and safety unknown. The short half-life of rivaroxaban combined with once daily dosing may be problematic if there are adherence concerns. There are concerns on how to best transition patients off of rivaroxaban as there was a noted increase in events after treatment discontinuation (see full prescribing information for transitioning patients from rivaroxaban to other anitcoagulants).

Efficacy and Safety Summary of Off-label Uses

Acute DVT and Continuation Treatment

- Rivaroxaban was studied in two poor quality studies for acute DVT and continuation treatment (EINSTEIN-DVT and EINSTEIN-EXTENSION). Currently, there is insufficient evidence to support rivaroxaban use for this indication and is not recommended until further data becomes available.

Acute Coronary Syndrome

- Most recently rivaroxaban was studied in patients presenting with Acute Coronary Syndrome (ACS) in the ATLAS ACS 2-TIMI 51. Patients were randomized to rivaroxaban 2.5mg twice daily, rivaroxaban 5mg twice daily or placebo, along with standard medical care for ACS.

There is moderate evidence to suggest rivaroxaban is better than placebo for this indication, however, there are no studies comparing the standard of care, aspirin and clopidogrel, to rivaroxaban. Doses used in this study are not currently available and use for this indication will need to be revisited in the future.

Cost Considerations:
Costs will be discussed in the executive session.

PDL Placement Recommendation:
There is low-strength of data to suggest that rivaroxaban is at least as effective as enoxaparin for prophylaxis of DVT in patients undergoing THR and TKR. The RECORD studies demonstrated efficacy favoring rivaroxaban, with the limitation of using the European dosing regimen in the one of the TKR studies, excluding high percentages of patients from analysis, and results being driven by asymptomatic DVTs. It is recommended that rivaroxaban be added to the PDL for this indication, after cost considerations are taken into account, and dose limitations should be applied.

There is one fair quality trial to demonstrating efficacy of rivaroxaban use in AF. Concerns over suboptimal warfarin use in ROCKET AF makes conclusions on relative efficacy and safety unknown. Efficacy relative to dabigatran has not been established. Warfarin is recommended as the first line agent for this indication.

BACKGROUND/CURRENT LANDSCAPE

FDA Approved Indication:Thromboprophylaxis after THR and TKR

For patients undergoing THR or TKR prophylactic anticoagulants are considered standard practice. A recent guideline by the American Academy of Orthopaedic Surgeons gives a moderate recommendation for the use of prophylactic pharmacological agents for VTE prevention in those patients that are not at elevated risk. Due to insufficient evidence they are unable to recommend any particular preventative strategy or treatment duration.[9] The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (CHEST) on antithrombotic and thrombolytic therapy recommends treatment with warfarin, LMWH, or fondaparinux for at least 10 days and up to 35 days for TKR and THR.[10] Oregon Health Plan (OHP) fee-for-service FFS currently lists LMWHs, enoxaparin and dalteparin, as preferred, and fondaparinux (Arixtra®) and tinzaparin (Innohep®) as not preferred. Desirudin (Iprivask®) is not managed via PDL and currently has no utilization restrictions. In the previous six months approximately 200 patients received short term anticoagulation (<45 days) accounting for almost 200 prescription claims (there were no claims for dabigatran or rivaroxaban).

FDA Approved Indication: Atrial Fibrillation

Patients with AF are at a four to five-fold increased risk of stroke and systemic embolism compared to those without AF.[11] Anticoagulants are a key component to managing patients with AF that are at an increased risk of stroke from cardioembolic events. The $CHADS_2$ risk stratification scheme is recommend to estimate stroke risk in patients with AF based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack (Table 1).[12] The greater the number of risk factors present, the greater the risk of stroke. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and suggest aspirin therapy for patients with up to one risk factor and treatment with a VKA for patients with one or more risk factors or in secondary prevention patients.[10] The guidelines also recommends VKA therapy for patients with a $CHADS_2$ score of ≥2.

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[12]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Off-label Uses: Acute/Chronic DVT

Acute DVT treatment is an additional indication for anticoagulation. DVT is a serious medical condition that affects 1 in 1000 people and can lead to PE and related risk of morbidity and mortality.[13] CHEST guidelines recommend initial treatment with LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days to bridge the patients to effective warfarin therapy, which should begin on the first treatment day.[10] Discontinuation of bridging should occur after the fifth day of therapy, provide the INR has been 2.0 or more for at least 24 hours. For patients with DVT or PE secondary to a reversible risk factor, the guidelines recommend treatment with warfarin for 3 months. Treatment recommendations for patients with unprovoked DVT or PE include warfarin for at least 3 months and up to a year or longer based on clinical judgment.

The VKA, warfarin, has served as the gold standard for oral anticoagulation and is a covered therapy, without restriction for OHP FFS patients. Approximately 350 patients utilized long term anticoagulation (>45 days), representing over 2,000 prescription claims within the last six months within the OHP population.

Off-label Uses: Acute Coronary Syndrome (ACS)

Antiplatelet drugs are used to prevent cardiovascular events and premature death in patients with multiple risk factors and in patients who have experienced Acute Coronary Syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction), transient ischemic attacks or thromboembolic stroke, or symptomatic peripheral arterial disease. Aspirin has been considered the gold standard. Aspirin is effective in reducing the occurrence of major cardiovascular events including death, recurrent myocardial infarction, recurrent angina, or progression to severe angina and nonfatal stroke. Several practice guidelines have been published that provide recommendations regarding the role of aspirin.[14,15,16,17,18,19] Limited trials with factor Xa and IIa inhibitors have been studied in patients after an ACS showing promising results in reduction of cardiovascular events.

CLINICAL PHARMACOLOGY

Rivaroxaban selectively blocks the active site of factor Xa, without a cofactor requirement (such as Anti-thrombin III) for activity. Blocking the conversion of factor X to factor Xa (FXa) inhibits intrinsic and extrinsic pathways that play a main role in the blood coagulation cascade.[1]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints

All Studies:	All-cause Mortality Major bleeding
DVT:	Recurrent VTE
DVT Prophylaxis:	PE Symptomatic VTE
AF:	Stroke
ACS:	Cardiovascular mortality Stent Thrombosis

Primary Study Endpoint:

RECORD 1-4: Composite of DVT, nonfatal PE and death
ROCKET-AF: Composite of stroke and systemic embolism
EINSTEIN-DVT and EINSTEIN-Extension: Recurrent VTE
ATLAS ACS 2-TIMI 51: Composite of death from cardiovascular causes, MI, or stroke

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2]	ARR / NNT[3]	Safety Results^	ARI / NNH[3]	Quality Rating[4]; Comments
RECORD 1[2]									
Eriksson B, et al Phase III, DB, RCT, PG, DD	1. **Rivaroxaban 10mg QD** (started after surgery) 2. **Enoxaparin 40mg SQ QD** (started evening before surgery)	Age: 63 yrs Female: 55% Prior VTE: 2.1-2.5% <u>Inclusion Criteria</u>; Scheduled for THR <u>Exclusion Criteria</u>: Bleeding, contraindications to anticoagulant use, pregnancy, lactation, severe liver or renal impairment, concomitant use of protease inhibitors or	1. n= 2209 2. n= 2224	Mean tx duration: 33 days F/U: 30-42 days after last dose	<u>Composite of DVT, nonfatal PE, or death:</u> R: 18 (1.1%) E: 58 (3.7%) RR 0.30 95% CI 0.12 to 0.51 <u>All-cause Mortality:</u> R: 5 (0.3%) E: 4 (0.3%) RR 1.22 95% CI 0.33 to 4.5 <u>PE:</u> R: 4 (0.3%) E: 1 (0.1%) RR 3.9	ARR 2.6% NNT 38 NS NS	<u>Major Bleeding:</u> R: 6 (0.3%) E: 2 (0.1%) RR 3.0 95% CI 0.61 to 14.9	NS	• Study Rating: Fair • Composite endpoint results driven by asymptomatic findings. • Large number of patients unaccounted for – sensitivity analysis states that missing data didn't effect power estimates • Symptomatic VTE similar in each treatment group (0.3% rivaroxaban and 0.5% enoxaparin) • Primary outcome was a composite endpoint including symptomatic and asymptomatic DVTS. The importance and clinical relevance of asymptomatic DVTs is unknown. • Per-protocol population was used for efficacy outcomes except symptomatic VTE which used mITT population.

		fibrinolytic agents			95% CI 0.44 to 35.0 <u>Symptomatic VTE:</u> R: 7 (0.3%) E: 15 (0.7%) RR 0.47 95% CI 0.19 to 1.15	NS	* Safety population used for above result		
RECORD2									
Kakkar A, et al Phase III, RCT, DB, DD	1. **Rivaroxaban 10 mg daily** (started 6-8 hrs. after wound closure) 2. **Enoxaparin 40mg SQ QD** (started 12 hours before surgery)	Age: 61 years Female: 53.7% <u>Inclusion</u>: Scheduled for THR <u>Exclusion</u>: See RECORD1	1. n= 864 2.n= 869	Rivaroxaban Tx: Mean 33.5 days Enoxaparin Tx: Mean 12.4 days F/U: 30-35 days after last dose of medication	<u>Composite of DVT + nonfatal PE or death</u> R: 17 (2.0%) E: 81 (9.3%) RR 0.21 95% CI 0.13 to 0.35 <u>All-cause Mortality:</u> R: 2 (0.2%) E: 8 (0.7%) RR 0.33 95% CI 0.07 to 1.7 <u>PE:</u> R: 1 (0.1%) E: 4 (0.5%) RR 0.25 95% CI 0.03 to 2.2 <u>Symptomatic VTE:</u> R: 3 (0.2%) E: 15 (1.2%) RR 0.20 95% CI 0.06 to 0.69	ARR 7.3% NNT 14 NS NS ARR 1.0% NNT 100	<u>Major bleeding</u> R: 1 (<0.1%) E: 1 (<0.1%) RR 1.0 95% CI 0.06 to 16.0	NS	• Study Rating: Poor • Composite endpoint results driven by asymptomatic findings • High number of excluded patients from mITT • Compared DVT events for 33 days of rivaroxaban versus 12 days for enoxaparin • Higher than expected invalidity rate for venograms – sensitivity analysis showed that didn't effect power • Increase number of cardiovascular events after rivaroxaban discontinuation

RECORD3[4]									
Lassen M, et al Phase III, RCT DB, DD	**1. Rivaroxaban 10mg QD** (started 6-8 hrs. after wound closure) 2. **Enoxaparin 40mg SQ QD** (started 12 hours before surgery)	Age: 67 years Female: 70% rivaroxaban / 66% enoxaparin Inclusion Criteria: Scheduled for TKR Exclusion Criteria: See RECORD1	1. n= 824 2. n=878	Tx duration: 10-14 days Venography: 11-15 days F/U: 30-35 days after last dose of tx	Composite of DVT, nonfatal PE, or death: R: 79 (9.6%) E: 166 (18.9%) RR 0.51 95% CI 0.39 to 0.65 All-cause Mortality: R: 0 (0%) E: 6 (0.5%) PE: R: 0 (0%) E: 4 (0.3%) Symptomatic VTE: R: 13 (1.1%) E: 27 (2.2%) RR 0.50 95% CI 0.25 to 0.94	ARR 9.2% NNT 11 NS NS NS	Major Bleeds: R: 7 (0.6%) E: 6 (0.5%) RR 1.2 95% CI 0.40 to 3.5	NS	• Study Rating: Fair • Utilized European dosing of enoxaparin 40mg daily for TKR • Anticoagulant allowed during follow-up period • Non-inferiority margin set at 4% • Only 67% of population used in mITT analysis
RECORD 4[5]									
Turpie A, et a Phase III, DB, RCT, DD	1. **Rivaroxaban 10mg QD** (started 6-8 hrs. after wound closure) 2. **Enoxaparin 30mg SQ BID** (started 12 hours postoperatively)	Age: 64 years Female: Rivaroxaban 66% Enoxaparin 64% Inclusion Criteria: Scheduled for TKR Exclusion Criteria: See RECORD1	1. 965 2. 959	Tx Duration: 10-14 days Follow-Up: 30-35 days after last dose	Composite of DVT + nonfatal PE or death: R: 67 (6.9%) E: 97 (10.1%) RR 0.67 95% CI 0.51 to 0.93 All-cause Mortality: R: 6 (0.1%) E: 6 (0.2%) RR 0.99 95% CI 0.32 to 3.1 PE: R: 5 (0.3%) E: 8 (0.5%) RR 0.62 95% CI 0.20 to 1.9	ARR 3.2% NNT 31 NS NS	Major bleeding: R: 10 (0.7%) E: 4 (0.3%) RR 2.5 95% CI 0.78 to 7.9	NS	• Study Rating: Poor • Composite endpoint results driven by asymptomatic findings • Data deemed not reliable by FDA due to compliance deficiencies with study procedures • Only 61% or patients eligible for primary endpoint analysis

					Symptomatic VTE: R: 14 (0.7%) E: 21 (2.0%) RR 0.66 95% CI 0.34 to 1.3	NS			
ROCKET AF[6]									
Patel M, et al Phase III, RCT DB, DD	1. **Rivaroxaban 20mg QD** 2. **Warfarin** (dose-adjusted to INR of 2.0-3.0)	Age: 73 yrs Female: 40% ASA use: 36% Mean $CHADS_2$ Score: 3.5 Coexisting Conditions: 55% Mean TTR for warfarin patients: 55% Inclusion: Nonvalvular a-fib with moderate to high risk of stroke Exclusion: Cardiac related conditions, active bleeding, uncontrolled hypertension, disabling stroke, chronic NSAID, anticoag tx, use of strong CYP3A4 inhibitors , contraindication t warfarin, severe renal or hepatic disease	1. 7081 2. 7090	Median Tx duration: 590 days Follow up: 707 days	Stroke or Systemic Embolism: R: 269 (2.1%) W: 306 (2.4%) HR 0.88 95% CI 0.75 to 1.03 P <0.001 for inferiority p=0.12 for superiority All Cause Mortality: R: 582 (4.5%) W: 632 (4.9%) HR: 0.92 95% CI, 0.82 to 1.03 P= 0.15	NS NS	Major Bleeds: R: 395 (5.6%) W: 386 (5.4%) HR 1.04 95% CI 0.90 to 1.20 P= 0.58	NS	• Study rating: fair • Warfarin INR values were • within the therapeutic range 55% which suggests suboptimal warfarin management • Information on management of INR was not provided • Results shown non-inferiority but unable to claim superiority to warfarin in ITT analysis • Rivaroxaban group had more strokes and embolisms during transition to open-label portion of study (ITT analysis) showing non-inferiority but not superiority • No component endpoint results provided • 32 patients lost to follow-up • 23.7% of patients in rivaroxaban group and 22.2% of patients in warfarin group discontinued treatment prior to an end point event or before the end of study • Concerns over short half-life and once daily dosing.
EINSTEIN-DVT[7]									
The Einstein	1. Rivaroxaban 15mg twice daily X 3 weeks then 20mg	Age: 56 years Female: 43%/44% Inclusion:	1. 1731	Median Tx duration: 3, 6, or 12 months	Recurrent VTE: R: 36 (2.1%) E-VKA: 51 (3.0%) HR 0.68		Major Bleeding: R: 14 (0.8%) E-VKA: 20 (1.2%) HR 0.65	NS	• Study Rating: Poor • Open label design lends results subject to bias • Patients on warfarin in TTR 58%

Investigators Phase III, RCT, Open-label, PG, non-inferiority study	once daily 2. Enoxaparin + either warfarin or acenocoumarol (vitamin K antagonist)	Acute symptomatic DVT Exclusion: Additional VKA indication, CrCl <30 ml/min, significant liver disease, active bleeding uncontrolled HTN, pregnant/breastfeeding concomitant CYP-450 3A4 inhibitors	2. 1718		95% CI 0.44-1.04 p<0.001 PE: R: 3 E-VKA: 6 All-cause mortality: R: 38 (2.2%) E-VKA: 49 (2.9%) HR 0.67 95% CI, 0.33 to 1.30		95% CI 0.33 to 1.30 p=0.21	NS	• 73% in rivaroxaban group and 71% in the warfarin group were pretreated with parenteral anticoagulants • Low dropout rates • Only symptomatic DVTs evaluated
EINSTEIN-Extension[7]									
The Einstein Investigators Phase III, DB, PG	1. Rivaroxaban 20mg daily 2. Placebo	Age: 58 yrs Female: 41%/43% Inclusion: objectively confirmed, symptomatic DVT or PE with 12 month prior treatment with warfarin or acenocoumarol Exclusion: additional VKA indication, CrCl <30 ml/min, significant liver disease, active bleeding, uncontrolled HTN, pregnant/ breastfeeding, concomitant CYP-450 3A4 inhibitors	1. 602 2. 594	Tx duration: 6 or 12 months	Recurrent VTE: R: 8 (1.3%) P: 42 (7.1%) HR 0.18; 95% CI 0.09 to 0.39 p<0.001 PE: R: 1 P: 0 All-cause mortality: R: 1 (0.2%) P: 2 (0.3%)	ARR 5.8% NNT 17	Major Bleeding: R: 4 (0.7%) P: 0 (0.0%) p=0.11	NS	• Study Rating: Poor • 53% of patients from previous studies – bias results to those already able to tolerate therapy • Placebo comparison limits clinical applicability • Lost to follow-up rates low

ATLAS ACS 2-TIMI 51 [8]									
ATLAS ACS 2-TIMI 51 Investigators RCT, DB, PC, Phase III	1. Rivaroxaban 2.5mg or 5mg twice daily 2. Placebo	Mean age: 61 yrs Males: 74-75% <u>Inclusion</u>: patients 18 and over with symptoms of ACS and STEMI, NSTEMI, or unstable angina. Those <55 also had DM or previous MI. NSTEMI: 50% ea.group STEMI: 26% ea. Group Unstable angina: 24% ea. group <u>Exclusion</u>: Reduced platelets and hemoglobin levels, CrC <30ml/min, previous bleeding, previous stroke or TIA on ASA o thienopyridine Also on standard medical therapy including low-dose ASA and thienopyridine	R 2.5mg 5174 R 5 mg 5176 Placebo 5176	Mean tx duration 13.1 months	<u>Composite of death from CV, MI or stroke:</u> R 2.5mg: 9.1% HR 0.84 95% CI 0.72 to 0.97 P= 0.007 P: 10.7% R 5mg: 8.8% HR 0.85 95% CI 0.73 to 0.98 P=0.01 P: 10.7% <u>CV Mortality:</u> R 2.5mg: 2.7% HR 0.66 95% CI, 0.51 to 0.86 P=0.005 P: 4.1% R 5mg: 4.0% HR 0.94 95% CI 0.75 to 1.20 P =0.57 P: 4.1% <u>Stent Thrombosis:</u> R 2.5mg: 2.2% HR 0.65 95% CI 0.45 to 0.94 P= 0.02 R 5mg: 2.3% HR 0.73 95% CI 0.51 to 1.04 P=0.04 P: 2.9%	ARR 1.6% NNT 63 ARR 1.9% NNT 53 ARR 1.4% NNT 71 NS ARR 0.7% NNT 143 ARR 0.6% NNT 166	<u>Major Bleeding:</u> R 2.5mg: 1.8% P: 0.6% HR 3.46 95% CI 2.08 to 5.77 P<0.001 R 5mg: 2.4% P: 0.6% HR 4.47 95% CI 2.71 to 7.36 P<0.001 <u>Intracranial Bleeds:</u> R 2.5mg: 14 (0.4% HR 2.83 95% CI 1.02 to 7.86 P= 0.04 P: 0.2% R 5.0mg: 18 (0.7% HR 3.74 95% CI 1.39 to 10.07 P=0.005 P: 0.2% <u>Fatal Bleeds:</u> R 2.5mg: 6 (0.1%) P: 9 (0.2%) HR 0.67 95% CI 0.24 to 1.89 P=0.45 P: 0.2% R 5mg: 15	ARI 1.2% NNH 83 ARI 1.8% NNH 56 ARI 0.2% NNH 500 ARI 0.5% NNH 200 NS	• Study Rating: Fair • Increased major bleeds and intracranial bleeds but fatal bleeds similar • Younger population studied. Potential for increased risk o bleeding in elderly. • Premature discontinuation i 29.4% of rivaroxaban and 26.4% of placebo

					All-cause mortality: R 2.5mg: 320 (9.3%) P: 153 (4.5%) HR 0.68 95% CI, 0.53 to 0.87 P=0.004 R 5mg: 321 (9.1%) P: 153 (4.5%) HR 0.95 95% CI, 0.76 to 1.19 P=0.89		(0.4%) P: 9 (0.2%) HR 1.72 95% CI 0.75 to 3.92 P= 0.20	NS	

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST-segment elevation myocardial infarction

Trial Details

DVT Prophylaxis

Rivaroxaban was approved for the prophylaxis of DVT and PE in over 9,500 patients undergoing total hip replacement (THR) and total knee replacement (TKR) based on data from four multi-center, RCTs; RECORD 1-4.[2,3,4] RECORD 1 and 2 enrolled patients scheduled for THR and RECORD 3 and 4 included patients scheduled for TKR. Patients were treated for a mean duration of 33 days in RECORD 1 and 2, 10-14 days in RECORD 3 and 4. Patients were randomized to rivaroxaban 10 mg daily, starting after surgery, or enoxaparin, starting on the evening prior to surgery. Enoxaparin doses were 40mg sq daily for RECORD 1-3 and 30mg sq twice daily in RECORD 4. The primary efficacy analysis was the composite of DVT, nonfatal PE and death with the primary safety analysis being major bleeding. The primary efficacy analysis results were based on a Modified Intent to Treat (MITT) population which included 8,512 patients (67%) of the original study population.

There was low to moderate-strength of evidence from RECORD 1 that rivaroxaban was similar to enoxaparin in regards to the component outcomes of all-cause mortality and non-fatal pulmonary embolism. There was also low to moderate-strength of evidence that rivaroxaban was more effective than enoxaparin in regards to incidence of DVTs (ARR -2.7%; 95% CI, -3.7 to -1.7; p<0.001). In RECORD 3 there was also low-moderate strength of evidence for no difference in all-cause mortality and non-fatal pulmonary embolism rates between rivaroxaban and enoxaparin. There was low to moderate-strength of evidence that rivaroxaban was superior to enoxaparin in regards to DVTs (ARR -8.4%; 95% CI, -11.7 to -5.2; p=<0.001). However, the use of the European enoxaparin dosing regimen of 40mg once daily in RECORD 3, limits the applicability of the results to United States patients were the recommended dosing regimen for DVT prophylaxis in patients undergoing TKR is 30mg twice daily. There was moderate-strength of evidence to suggest major bleeding rates were higher for rivaroxaban compared to enoxaparin in both RECORD 1 and 3 studies, although not statistically significant.

The Canadian Agency for Drugs and Technologies in Health (CADTH) recommend rivaroxaban as an effective treatment option for VTE prophylaxis after THR or TKR, as an alternative to enoxaparin, with no compelling evidence to suggest an increased incidence of adverse effects.[21]

RECORD 2 and 4 were deemed poor studies due to FDA analysis stating data was unreliable. RECORD 2 compared rivaroxaban to enoxaparin, using different durations of treatment, which limit the applicability of the efficacy conclusions.[20] One of two clinical investigators confirmed data from RECORD 4 was not considered reliable in support of the New Drug Application (NDA). Two additional clinical investigator inspections were conducted prior to the NDA submission, regarding RECORD 2 and RECORD 4, and found that data from both these sites were unreliable. After an analysis of all the RECORD studies, with removal of questionable data, the FDA found efficacy results favoring rivaroxaban, driven by asymptomatic DVTs detected by venography.

Atrial Fibrillation

ROCKET AF was a phase III, DB, DD, RCT in over 14,000 patients in 45 countries with nonvalvular atrial fibrillation who were at moderate to high risk of stroke. Patients were randomly assigned to rivaroxaban 20mg daily or dose-adjusted warfarin (INR 2.0-3.0). Participants had a median age of 73 years and 60% were male. The mean $CHAD_2$ score was 3.5 and 55% of participants had coexisting conditions. The median treatment duration was 590 days with 707 days of follow-up. The primary efficacy analysis was the composite of stroke (ischemic and hemorrhagic) and systemic embolism. A noninferiority analysis (margin of 1.46) was preformed on the per-protocol population. If noninferiority was achieved then noninferiority and superiority testing would be performed on the ITT population. The major safety endpoint was composite of major and nonmajor clinically relevant bleeding events. Major bleeds is reported as the more clinically relevant safety endpoint.[6]

There was low-strength of evidence from ROC KET AF that rivaroxaban was noninferior to warfarin for the composite outcome of stroke and systemic embolism (HR 0.88; 95% CI, 0.75 to 1.03; p<0.001 for noninferiority, p=0.12 for superiority). There was low-strength of evidence that major bleeding rates were similar between rivaroxaban and warfarin (HR 1.04; 95% CI, 0.90 to 1.20, p=0.58) and intracranial bleeds were less with rivaroxaban. TTR was only 55% for warfarin patients in ROCET-AF. Concerns over suboptimal use of warfarin make conclusions on comparable efficacy and safety difficult. There is insufficient evidence comparing rivaroxaban to well controlled warfarin management. The short half-life of rivaroxaban combined with once daily dosing may be problematic if there are adherence concerns.

Off-label Uses

DVT Treatment

Rivaroxaban was studied in a phase III, parallel group, non-inferiority, open-label, RCT in over 3,400 patients with acute symptomatic DVT without PE in the EINSTEIN-DVT trial. Patients were randomized to rivaroxaban 15mg twice daily for 3 weeks and then 20mg once daily or enoxaparin and a vitamin K antagonist (warfarin or acenocoumarol) for 3, 6, or 12 months.[7]

There was low-strength of evidence that rivaroxaban was non-inferior to standard treatment (enoxaparin plus VKA) for the prevention of recurrent VTE in patients with acute DVT. The primary endpoint was experienced by 2.1% of the rivaroxaban group and 3.0% for the enoxaparin/VKA group (HR 0.68; 95% CI, 0.44-1.04; p<0.001 for noninferiority). There was low-strength of evidence of similar rates of major bleeding ,8.1% in both groups.

The EINSTEIN-EXTENSION study was a PC, double-blind, phase III continuation study in over 1,000 patients with a confirmed symptomatic DVT or PE previously treated with a VKA or rivaroxaban for 6 or 12 months (EINSTEIN-DVT, EINSTEIN-PE(ongoing)), that there was equipoise with respect to the need for continued anticoagulation. Patients were randomly assigned to rivaroxaban 20mg daily or placebo for an additional 6 or 12

months. The average patient was 58 years old with around 40% being female. The primary efficacy analysis was recurrent venous thromboembolism and major bleeding was the primary safety analysis.[7]

There is low-strength of evidence that rivaroxaban is more effective than placebo in preventing VTE with extended treatment (HR 0.18; 95% CI 0.09 to 0.39; p<0.001). There is also low-strength of evidence that rivaroxaban causes more major bleeding than placebo. Extension study design may bias efficacy and safety results based on enrollment of patients already able to tolerate/respond to treatments.

Acute Coronary Syndrome

The ATLAS ACS 2-TIMI 51 study was a DB, PC, RCT involving 15,526 patients in 44 countries presenting with Acute Coronary Syndrome (ACS) and an ST-segment elevation myocardial infarction (NSTEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. Patients were randomized to rivaroxaban 2.5mg twice daily, rivaroxaban 5mg twice daily or placebo, along with standard medical care for ACS. Patients were treated for a mean duration of 13.1 months. The primary efficacy endpoint was a composite of death from cardiovascular causes, myocardial infarction or stroke.[8]

There was moderate-strength of evidence that rivaroxaban 2.5mg decreased cardiovascular death, MI and all-cause mortality rates compared to placebo, being statistically significant for cardiovascular mortality and all-cause mortality. Rivaroxaban 5 mg twice daily decreased cardiovascular mortality and MI compared to placebo with moderate-strength of evidence, with only MI rates being statistically significant. There was moderate-strength of evidence that rivaroxaban 2.5mg and 5mg twice daily increased the risk of stroke, although neither were statistically significant. There was moderate strength of evidence that rivaroxaban increases the risk of major bleeds. There were also noted increases in intracranial bleeds, compared to placebo, in both rivaroxaban treatment groups, with a NNH of 500 and 200 in the 2.5mg and 5mg groups, respectively. The average age of study participant was 62 years old, which makes extrapolating results to a more elderly population difficult.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):

As with other anticoagulants, rivaroxaban may cause epidural or spinal hematomas in patients whom are receiving neuraxial anesthesia. Active major bleeding and hypersensitivity are contraindications to rivaroxaban therapy.[1]

Rivaroxaban should be used cautiously in patients with bleeding disorders, severe hypertension, pregnancy and renal and hepatic impairment. Other serious adverse events described in post-marketing reports include cerebral hemorrhage, epidural hematoma, and hypersensitivity reactions including anaphylactic shock, agranulocytosis and Steven-Johnson Syndrome.[1,20]

In patients with AF, discontinuing rivaroxaban treatment has put patients at increased risk of thrombotic events. In ROCKET AF an increased risk of strokes were seen following rivaroxaban discontinuation. Consider continuing patients on another anticoagulant if rivaroxaban is to be discontinued.[1]

Bleeding: Rivaroxaban increases the risk of bleeding and can cause significant or even fatal bleeding in certain patients. The risk for bleeding increases when other drugs that also increase the risk of bleeding are used concurrently and was most common during the first week of surgery. Rivaroxaban should be used with caution in pregnant women due to pregnancy related hemorrhage.[1]

In trials evaluating rivaroxaban for prophylaxis in patients undergoing hip or knee replacement bleeding was the most common adverse event. Major bleeding events were higher with rivaroxaban in the RECORD trials compared to enoxaparin, 0.39% vs. 0.21%, respectively.[20]

Table 2.0 Bleeding Events in Patients Undergoing Hip or Knee Replacement Surgeries[1]

Total Treated Patients in Record 1-3*	Rivaroxaban 10mg N= 4487 (n/%)	Enoxaparin 40mg Daily† N=4524 (n/%)
Major Bleeding Event	14 (0.3)	9 (0.2)
Fatal Bleeding	1 (<0.1)	0
Bleeding into a Critical Organ	2 (<0.1)	3 (0.1)
Bleeding that Required Re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding Requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any Bleeding Event**	261 (5.8)	251 (5.6)

* Data from RECORD 4 excluded from pooled data

** Includes major bleeding events.

† Includes placebo-controlled period for RECORD2

Tolerability (Drop-out rates, management strategies):

Overall rivaroxaban was well tolerated with similar discontinuation rates as enoxaparin, 3.7% and 4.6%, respectively.

Pregnancy/Lactation rating:

Rivaroxaban is rated Pregnancy Category C. Dosing hasn't been studied in pregnant women and it should only be given if the potential benefit outweighs the risk to the mother and fetus.[1] Rivaroxaban was shown to be secreted into milk when studied in rats.

Unanswered safety questions:
The safety of taking rivaroxaban long term is unknown. There is no antidote for rivaroxaban in a bleeding emergency. Bleeding should be managed by holding rivaroxaban treatment and giving recombinant factor VIIa or activated prothrombin complex concentrate could be considered, although not studied. Prothrombin complex concentrate has been shown to be effective in a small population but additional data is needed.[22] Protamine and vitamin K would not be expected to reverse anticoagulant effects of rivaroxaban.[23] Of concern was an increased incidence of cardiovascular events during the follow-up period in ROCET AF in the rivaroxaban group compared to warfarin. This increase was thought to be due to a gap in protective effect during drug transition off of rivaroxaban and to warfarin after study completion.[6]

Dose Index (efficacy/toxic):
DVT Prophylaxis
For most patients the dose of rivaroxaban 10mg daily, without regards to meals is recommended. The initial dose should be taken 6-10 hours post surgery once hemostasis has been established. Treatment should continue for 35 days for patients undergoing hip replacement surgeries and 12 days for patients undergoing knee replacement surgeries.

Nonvalvular Atrial Fibrillation
Rivaroxaban is given as 20 mg with the evening meal, for patients with CrCl >50 mL/min. For patients with CrCl of 15 to 50 mL/min a dose of 15 mg with the evening meal is recommended. Rivaroxaban is not recommended for a CrCL of <15 mL/min.

Increased exposure to rivaroxaban was noted in elderly patients, which may be due to age related changes in renal function. Avoid using rivaroxaban in patients with a CrCl <30 mL/min. Patients with moderate renal failure (CrCl 30-<50 mL/min) should be observed closely for bleeding. Due to significant increases in rivaroxaban concentrations with impaired hepatic function, patients with moderate (Child-Pugh B), severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy should not take rivaroxaban. For patients with renal insufficiency (CrCl 15-50 mL/min) taking rivaroxaban for AF the recommended dose is 15mg once daily, with the evening meal.

Rivaroxaban absorption is dependent upon the site of drug release in the GI tract. Drug delivery directly to the proximal small intestine (e.g., feeding tube) can result in reduced drug absorption.[1]

Monitoring:
Dose –dependent inhibition of Factor Xa and in prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are prolonged dose-dependently. Rivaroxaban also influences Anti-factor Xa activity.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	MicroMedex	ISMP	Clinical Judgment
LA/SA for rivaroxaban (generic)	None	None	None	None	None
LA/SA for Xarelto (brand)	None	None	None	None	None

Adverse Events Reported in ≥1% of Rivaroxaban Treated Patients in RECORD trials 1-3[1]

Adverse Events (1) (MedDRA System Organ Class and Preferred Term)	Rivaroxaban 10mg n (%)	Enoxaparin 40mg Daily† n (%)
Number of Patients	**n=4487**	**n= 4524**
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0))
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous System Disorder		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

† Includes placebo-controlled period for RECORD 2

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Rivaroxaban 10mg for DVT prophylaxis prior to TKR or THR Rivaroxaban 20mg once daily for AF	Tablet	Oral	Once daily	DVT Prophylaxis: Use cautiously in moderate renal impairment (CrCl 30-50 ml/min) Do not use in severe renal impairment (CrCl <30 ml/min) Nonvalvular Atrial Fibrillation: CrCl 15-50 ml/min give 15mg once daily Avoid if CrCl 30-50 ml/min.	Avoid use in moderate or severe hepatic impairment or in hepatic disease with coagulopathy	N/A	Increased rivaroxaban concentrations were seen in elderly patients, perhaps due to age-related changes in renal function. Renal function assessment should be considered in patients ≥65 years old.	- Tx duration of 35 days recommended for hip replacement surgery - Tx duration of 12 days recommended for knee replacement surgery - Absorption is increased with food and is recommended for AF dosing

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability*	10mg dose: 80-100% (not affected by food)
	20mg dose: 66% (fasting), increases with food
Protein Binding	92-95%
Elimination	66% urine, 28% feces
Half-Life	5-9 hours
Metabolism	Oxidative degradation and hydrolysis via CYP3A4/5 and CYP2J2 Substrate of transporter proteins P-gp and ABCG2

* Dose-dependent absolute biovailability

ALLERGIES/INTERACTIONS

Drug-Drug:

Rivaroxaban is a substrate for CYP3A4, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors or inducers of these enzymes/transporters may change rivaroxaban exposure. Concomitant use of rivaroxaban with drugs that are combined p-glycoprotein (P-gp) and strong CYP3A4 inducers (carbamazepine, phenytoin, rifampin, St.John's wort) should be avoided. Avoid rivaroxaban use with P-gp and strong CYP3A4 inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir and conivaptan) which significant increases in rivaroxaban exposure has been observed, which may increase bleeding risk.[1]

When using rivaroxaban for prophylaxis of DVT, if data suggests a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin) then no precautions are necessary when using rivaroxaban concomitantly with P-gp and CYP3A4 inhibitors.

Rivaroxaban should not be used with other anticoagulants. Use with clopidogrel should be avoided unless the benefit outweighs the bleeding risk. Promptly evaluate any signs or symptoms of blood loss. No pharmacokinetic or pharmacodynamic interactions have been noted with naproxen or aspirin but safety of coadministration long-term has not been studied.[1]

It is not recommended that rivaroxaban be used with NSAIDS due to an increased risk of bleeding. Caution is advised when treating patients concomitantly with aspirin, other platelet aggregation inhibitors or NSAIDS.[1]

Food-Drug:

No food-drug interactions have been reported.[1]

Allergy/Cross Reactive Substances:

In the RE-LY trial, drug hypersensitivity was reported in <0.1% of patients. No cross-sensitivities have been reported.[1] Postmarketing reports of anaphylaxis to rivaroxaban have occurred. Do not use in patients with severe hypersensitivity reactions to rivaroxaban.

APPENDIX:
Suggested PA Criteria

Oral Direct Factor Xa Inhibitors

Goal(s):

- Promote safe and effective therapies for oral direct factor Xa inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis requiring short-term (<45 days) anticoagulation (i.e. total knee replacement or total hip replacement)?	**Yes: Yes:** Approve for 12 days for TKR. Approve for 35 days for THR.	**No:** Go to #2
2. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes**: Go to #3	**No:** Deny. (Medical appropriateness)
3. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Approve. Additional information can be found at: http://www.dhs.state.or.us/policy/healt	**No:** Go to #4

Message: • Preferred products do not require PA for <4 days/week. • Preferred products have received evidence-based reviews for comparative effectiveness and safety by the Health Resources Commission (HRC). http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml	hplan/guides/pharmacy/clinical.html	
4. Is the patient unable to take preferred oral anticoagulants due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for up to 1 yr.	**No:** Deny. Recommend trial of preferred anticoagulants.

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Hepatitis C Class Review

Month/Year of Review: January 2012
PDL Class: Hepatitis C Agents
Suggested Revision: Expand current Hepatitis C PDL class to include all agents for treatment of Chronic Hepatitis C (CHC) Virus

Current Status of PDL Class:
PA Criteria for Pegylated Interferon and Ribavirin (Appendix 1)
Preferred Agents: Pegasys (peginterferon alfa 2a), Pegintron (peginterferon alfa 2b)

Background:
Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and death from liver disease and leading indication for liver transplantation in the United States (U.S.). Therefore, the goal of therapy for HCV infection is to prevent complications and death.[1]

An estimated 180 million people worldwide are infected with HCV. The prevalence of HCV infection in the U.S. between 1999 and 2002 was 1.6%, or about 4.1 million people positive for hepatitis C antibody (anti-HCV).[1]

About 55% to 85% of those who develop acute hepatitis C remain infected, rather than achieve spontaneous resolution.[1] An estimated 15 to 30% of patients with CHC develop cirrhosis within 30 years. One to three percent of patients per year with HCV-related cirrhosis develop hepatocellular carcinoma.[2]

U.S. guidelines have recommended combination peginterferon alfa (P) and ribavirin (R) as the standard of care (SOC) for CHC, with the optimal duration of treatment based on viral genotype. Response to treatment (i.e., SVR) with SOC is about 50% for Caucasians and 30% for African-Americans. Guidelines for treating HCV genotype 1 (HCV-1) were updated in fall 2011, following FDA approval of the direct acting antivirals (DAA) boceprevir (BOC) and telaprevir (TVR).[1,2]

HVC is classified into at least 6 major genotypes: genotype 1 (with subtypes 1a and 1b), which is the most common in the U.S.; genotypes 2 and 3, which are the next most common; and genotypes 4, 5, and 6, which are, thus far, the least common.[1] Genotype 1 accounts for >70% of CHC in the

U.S. and Europe and has the poorest response to treatment. Genotyping HCV is useful for predicting the likelihood of response to and duration of therapy.[3]

According to AASLD guidelines, widely accepted criteria for CHC treatment include HCV RNA serum positive, significant fibrosis, compensated liver disease, acceptable blood and biochemistry indices, willingness to be adherent to therapy, and no contraindications. Criteria contraindicating therapy include uncontrolled major depression, solid organ transplant, autoimmune hepatitis or autoimmune condition exacerbated by PR, untreated thyroid disease, pregnancy, inadequate contraception, severe concurrent medical illnesses, age <2, and hypersensitivity to drug therapies. However, these are not absolute and clinical judgment should be exercised in each case.[1]

Sustained virologic response (SVR) is associated with permanent virologic cure, long-term clearance of HCV infection, as well as improved morbidity and mortality in the vast majority of patients. RVR predicts a high likelihood of achieving an SVR. Those who achieve an RVR have an SVR rate of about 90%; however, only 15% to 20% of those with HCV-1 infection achieve RVR with peginterferon alfa. Early virologic response (EVR) is the most accurate predictor of non-response, as 97 to 100% of treatment-naïve HCV-1 patients who fail to reach EVR fail to achieve SVR. While end-of-treatment response (ETR) is an inaccurate predictor of achieving SVR, ETR is necessary for SVR to occur.[1,4]

On-treatment viral kinetics is used to guide the duration of therapy.[4] Studies have previously established patients with HCV-1 should be treated for 48 weeks with PEG-2a (180 µg/week sc) plus weight-based RIB (1000 or 1200 mg per day) or PEG-2b (1.5 µg/kg sc) plus weight-based RIB (800 mg, 1000 mg, 1200 mg, or 1400 mg).[7] Treatment may be discontinued in patients who do not achieve EVR. Forty to fifty percent of patients with HCV-1 treated with PEG and the standard weight-based dose of RIB for 48 weeks achieve SVR. The two FDA-approved PEGs (Pegasys, Roche, and PegIntron, Merck) have had similar efficacy and safety profiles in head-to-head comparisons.[4]

Summary:

The standard of care for the treatment of Chronic Hepatitis C (CHC) has been pegylated interferon (alfa 2a or alfa 2b) in combination with weight-based ribavirin (PR) for either 48 weeks or 24 weeks depending on genotype[1]. The American Association for the Study of Liver Disease recently published an update on the treatment of genotype 1 chronic hepatitis c virus infection guidelines to include the new direct acting antiviral (DAA) agents of BOC and TVR.[2] These were based on a review and analysis of published literature, guideline policies, and expert opinion. There is evidence showing a significant improvement in SVR rates in patients with genotype 1 CHC but the guidelines state that the recommendations are based on new data that is still quite limited and as more studies are conducted and become available the recommendations may need to be reconsidered.[2] Both BOC and TVR have evidence showing a significant improvement in demonstrating higher rates of virologic response compared with the current standard of treatment and also both in patients who had previously failed dual therapy, but at a significantly higher cost and with safety concerns including anemia, drug interactions, skin rashes, and adverse events[5].

The updated guidelines state:

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. (Class 1, Level A)
2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. (Class 1, Level A).

The combination of pegylated interferon and ribavirin remains the standard of care for all other genotypes.[1] Oregon reviewed the interferons for CHC previously and developed PA criteria for treatment with peginterferon and ribavirin shown in Appendix 1. Both Peg-Intron and Pegasys are listed as preferred agents. There is comparative effectiveness evidence demonstrating that there are no significant differences in efficacy or safety between the two agents.[4] The introduction of these long-acting peginterferons has become the standard of care and have replaced the older non-pegylated infererons[1].

In 2010, the FDA approved an expanded indication for interferon alfacon-1 (Infergen) for retreatment of CHC in combination with ribavirin after failure to previous treatment with a pegylated interferon and ribavirin[6]. This approval was based on a single study (DIRECT trial) which was a randomized, open-label, study comparing the safety and efficacy of two doses of interferon alfacon-1 plus ribavirin in previous nonresponders[4]. The AASLD guidelines do not demonstrate any role of interferon alfacon-1 in the treatment of CHC and there is limited data to support its use.

There is currently no comparative evidence evaluating if there is a difference in either efficacy or safety between BOC and TVR. There were also differences in how the drug studies were conducted as well as major differences in side effect profiles, making a direct comparison difficult. Only telaprevir was studied in prior null responders to PR therapy, BOC was studied in combination with peginterferon alfa-2b while TVR was given with peginterferon alfa-2a, and although there is a high incidence of anemia associated with both drugs it was managed differently in clinical trials. Use of erythropoietin stimulating agents (ESAs) was excluded from TVR studies while ESAs were allowed for the management of anemia at the discretion of the clinician in the BOC studies.[2,3] Ongoing studies are further evaluating how the management of anemia including ESA use or R dose reduction affects outcomes with BOC treatment.

Recommendations:

- Expand current Hepatitis C antiviral PDL class to include all agents for treatment of Chronic Hepatitis C Virus
- Recommend to maintain either one or both of peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (PegIntron) as preferred pegylated interferon products depending on price. These two agents are recommended in the current guidelines and have shown to be similar in terms of safety and efficacy.
- Designate interferon alfacon-1 (Infergen) as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.
- Develop PA criteria to support the judicious use of the oral protease inhibitors in patients with genotype 1 CHC in combination with pegylated interferon and ribavirin.

APPENDIX 1: Prior authorization criteria for pegylated interferon and ribavirin

Pegylated Interferon and Ribavirin

Goal(s):

Cover drugs only for those clients where there is medical evidence of effectiveness and safety

Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months

Requires pa: All drugs in HIC3 = W5G

Approval Criteria		
1. Is peginterferon requested preferred?	**Yes:** Go to #3.	**No:** Go to #2.
2. Will the prescriber consider a change to a preferred product? Message: - Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	**No:** Go to #3.
3. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code: (571.40; 571.41; 571.49)	**Yes:** Go to #4.	**No:** Go to #10
4. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #5
5. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment? Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.	**Yes:** Forward to DMAP Medical Director	**No:** Go to #6
6. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy? • severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy~~cytopenias~~ • untreated hyperthyroidism • severe renal impairment or transplant	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #7

• autoimmune disease • pregnancy • unstable CVD		
7. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes:** Go to #8	**No:** Deny; Pass to RPH (Medical Appropriateness)
8. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date:	**Yes:** Go to #9	**No:** Deny; Pass to RPH (Medical Appropriateness)
9. Does the patient have a documented HCV Genotype? Record Genotype:	**Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only	**No:** Deny; Pass to RPH (Medical Appropriateness)
10. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?	**Yes:** Go to #11	**No:** Deny; Pass to RPH (Medical Appropriateness)
11. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #12
12. Has the member received previous treatment with pegylated interferon?	**Yes:** Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

Continuation of Therapy- HCV

1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?

Yes: Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

Genotype	Approve for	Apply
1 or 4	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).
2 or 3	**An additional 12 weeks** or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).
For all genotypes and HIV co-infection	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).

No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

Clinical Notes:

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.

Stage is indicative of fibrosis:			Grade is indicative of necrosis:	
Stage 0	No fibrosis			
Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild

Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate
Stage 4	Cirrhosis		Stage 4	Marked

The following are considered investigational and/or do not meet medical necessity criteria:

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ ~~Re-treatment of HCV or HBV previous non-responders or relapsers~~
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

References:

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3. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 202258Orig1s000 summary review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000SumR.pdf. Accessed September 26, 2011.

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5. Tungol A, Rademacher K, Schafer JA. Formulary management of the protease inhibitors boceprevir and telaprevir for chronic hepatitis C virus. *J Manag Care Pharm*. 2011;17(9):685-694.

6. Infergen Package Insert. Kadmon Corporation, LLC. Available at: http://kadmon.com/files/infergen-pi.pdf.

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Month/Year of Review: January 2012
Generic Name: Telaprevir
Brand Name: Incivek™
PDL Class: Hepatitis C Antivirals

End date of literature search: 4th Quarter 2011
Manufacturer: Vertex Pharmaceuticals
Dossier received: Yes
Comparator Therapies: peginterferon alfa-2a plus ribavirin (PR) alone

FDA Approved Indications:[1] Telaprevir is indicated in combination with peginterferon alfa (P) and ribavirin (R) for treating genotype 1 chronic hepatitis C (CHC) in adult patients who:
• have compensated liver disease, including cirrhosis.
• are treatment-naïve or previously have been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.

Summary: American Association for the Study of Liver Diseases (AASLD) guidelines recommend triple therapy with telaprevir (TVR) in combination with PR as first-line treatment for genotype 1 CHC. Evidence for use of triple therapy comes from six phase 2 and three phase 3 studies.[2, 3] Moderate level evidence shows triple therapy is superior to PR therapy at producing a sustained virologic response (SVR).

The ADVANCE trial established that a treatment regimen including TVR for 12 weeks and PR for 24 weeks is superior to PR alone in treatment-naive patients who have achieved extended rapid virological response (eRVR) by week 4, while 48 weeks of PR with 12 weeks of TVR is recommended in patients not achieving eRVR. The difference in sustained virologic response (SVR) rate for triple therapy with 12 weeks of TVR versus PR alone in treatment-naïve patients was 31%, giving a number needed to treat (NNT) of 3. The ILLUMINATE trial established treating treatment-naïve patients who had achieved eRVR with more than 24 weeks of PR in combination with TVR provided no advantage. The REALIZE trial supports the use of TVR-containing regimens in patients previously treated with PR alone. Although results varied based on type of previous response, the overall difference in SVR rate for triple therapy with 12 weeks of TVR versus PR alone in previously treated patients was 47%, giving a number needed to treat (NNT) of 2.[3–6]

Data are compelling despite some internal and external validity concerns leading to "fair" quality assessment ratings for phase 3 studies. Also, questions are outstanding with regard to dosing and response in special populations and with regard to managing therapy in a general clinical setting and CHC population, given the careful monitoring for response, safety, and treatment adherence required for therapy.

The incidence of adverse reactions with triple therapy, and even for PR alone, are quite high and largely driven by the rates of rash (56%), fatigue (56%), pruritus (47%), nausea (39%), anemia (36%), and diarrhea (26%). Treatment is complicated and requires patient adherence and timely laboratory monitoring. Triple therapy is also very expensive necessitating judicious use of these agents in patients.

The benefits of triple therapy include improved SVR rates for patients as a whole, improved SVR rates for difficult-to-treat patients, shorter duration of therapy for treatment-naïve patients who achieve SVR, and, a re-treatment option for patients who have failed previous therapy with PR.

PDL Placement Recommendation:

- Recommend TVR require prior authorization to limit its use to treatment in genotype 1 HCV with clinical, dose, duration limits (Appendix 1).
- Consider other considerations such as duration of therapy, complexity of dosing regimen, pill burden, side effect profile, and evidence in previous null responders when evaluating both TVR and BOC.
- Due to high cost of treatment and lack of comparative effectiveness evidence, recommend evaluating OHA costs for both BOC and TVR for consideration of OHA management.

BACKGROUND/CURRENT LANDSCAPE

CHC Treatment response is defined by surrogate biochemical, histological, and virological parameters, rather than clinical endpoints such as liver disease and death, because the natural history of CHC evolves over decades.[7] Short-term outcomes include normalization of serum ALT levels, >2 point improvement in necroinflammatory score with no worsening in fibrosis score, and clearance of HCV RNA from serum as measured by PCR.[7]

Virological parameters are divided into the following:[7,8]

- sustained virological response (SVR): the absence of HCV RNA from serum by PCR 24 weeks after discontinuing therapy;
- end-of-treatment response (ETR): undetectable virus at the end of either a 24-week or 48-week course of therapy;
- rapid virological response (RVR): undetectable HCV RNA at week 4 of treatment (lower limit of detection 50 IU/mL by PCR);

- extended rapid virological response (eRVR): undetectable HCV RNA at weeks 4 and 12 (lower limit of detection 10 IU/mL by PCR used in ADVANCE trial [6]);
- early virological response (EVR): a ≥2 log reduction in or complete absence of serum HCV RNA at week 12 of therapy compared with the baseline level;
- virological breakthrough: the reappearance of HCV RNA while still on therapy;
- virological relapse: the reappearance of HCV RNA in serum following treatment discontinuation and documented ETR;
- null responders: patients who fail to suppress serum HCV RNA by at least 2 logs after 24 weeks of therapy (12 weeks in REALIZE trial[5]);
- partial non-responders: patients whose HCV RNA levels decreased by ≥2 logs IU/mL but never became undetectable at 24 weeks (12 weeks in REALIZE trial[5]); and
- non-responders: patients who fail to clear HCV RNA after 24 weeks of therapy.

Since the introduction of DAAs, AALD guidelines from the have been updated and state:[2]

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. (Class 1, Level A)
2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. (Class 1, Level A).

AASLD dosing guidelines are as follows:
1. The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin (Class 1, Level A).
2. Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks (Class 2a, Level A).
3. Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B).
4. Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1, Level A).
5. Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin (Class 2b, Level B).

6. Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C).

AALD recommendations with regard to stopping treatment are as follows:
1. Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (Class 2a, Level B).
2. Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).
3. Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (Class2a, Level A).
4. Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if biological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed (Class 1,Level A).
5. Patients who fail to have a biological response, which experience biological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (Class 2a, Level C).

AASLD dosing guidelines are as follows:
3. The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (Class 1, Level A).
4. Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B).
8. Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B).
10. Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1, Level A).
12. Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C).

AASLD recommendations with regard to stopping treatment are as follows:

5. Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (Class 2a, Level B).
13. Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).
15. Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (Class2a, Level A).
16. Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if biological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed (Class 1,Level A).
17. Patients who fail to have a biological response, who experience biological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (Class 2a, Level C).

CLINICAL PHARMACOLOGY[1]

TVR is a reversible, DAA against HCV. TVR works by selectively inhibiting the HCV NS3/4A serine protease, which is essential for the production of nonstructural proteins NS4A, NS4B, NS5A, and NS5B and for viral replication. Several NS3 amino acid substitutions confer resistance to TVR. V36M/A/L, T54A/S, R155K/T, and A156S/T variants emerged most frequently in biological failure and relapse patients.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:
1) Sustained virological response (SVR)
2) Relapse
3) Withdrawals due to adverse effects
4) Anemia
5) Rash/Pruritus

Primary Study Endpoint: 1) Sustained virological response

Evidence Table

Ref./Study Design[1]	Drug Regimens	Patient Population	N	Duration (weeks)	Efficacy Results[2] (CI, p-values)	ARR/NNT[3]	Safety Results^ (CI, p-values)	ARR/ NNH[4]	Quality Rating/Comments
ADVANCE									Fair
Jacobson 123 center Phase 3 Feb to Jun 2007 RCT, PC, DB, stratified	1. T12PR: telaprevir (T) (750 mg q8h) plus peginterferon alfa-2a (P) (180 µg per week) and ribavirin (R) (1000 mg qd for weight <75 kg or 1200 mg qd for weight ≥75 mg) for 12 weeks. Extended rapid virologic response (eRVR) patients received additional 12 weeks PR and others 36 weeks 2. T8PR: T plus PR for 8 weeks then PR plus PLA for 4 weeks. eRVR patients received additional 12 weeks PR and the others 36 weeks 3. PR (control): PR plus placebo (PLA) 12 weeks, then PR for 36 weeks Note: doses are the same for each drug in all arms.	Inclusion criteria: • aged 18–70 • chronic HCV genotype 1 • no previous treatment Exclusion criteria: • HIV or HBV positive • significant liver disease (e.g., cancer, decompensation) • absolute neutrophil count <1500 per ml^3, platelet count <90K per ml^3, hgb <12 g/dL women or <13 g/dL men Patient characteristics: Age (mean): 49 yrs Male: 58% White: 88% Black: 9% Hispanic: 11% HCV RNA ≥800K IU per ml: 77% HCV genotype 1a: 58% HCV genotype 1b: 41% HCV genotype unk: <1% Cirrhosis: 6% Bridging fibrosis: 15% Stratified for genotype 1 subtyp (a, b, unknown) and baseline HCV RNA <800K IU/mL or ≥800K/mL	1. 363 2. 364 3. 361 modified ITT	Treatment duration 24 or 48 weeks. Primary outcome assessed 24 weeks after end of treatment (i.e., week 48 or 72)	<u>Sustained virological response:</u> 1. T12PR: 75% PR: 44% (p<0.001) 2. T8PR: 69% PR: 44% (p<0.001) Other relevant endpoints: eRVR 1. T12PR: 58% 2. T8PR: 57% 3. PR: 8% Relapse among patients with undetectable HCV RNA at end of treatment period: 1. T12PR: 9% 2. T8PR: 9% 3. PR: 28%	31% / 3 (CI: 18–32) 25% / 4 (CI: 18–32) 50% / 2 49% / 2 19% / 5 19% / 5	Rash 1. T12PR: 37% 2. T8PR: 35% 3. PR: 24% Pruritus: 1. T12PR: 50% 2. T8PR: 45% 3. 3. PR:36% Anemia: 1. T12PR: 37% 2. 2. T8PR: 39% 3. 3. PR: 19% All-drug discontinuation due to adverse reaction: 1. T12PR: 10% 2. T8PR: 10% 3. PR: 7%	13% / 8 11% / 9 14% / 7 9% / 11 18% / 6 20% / 5 3% / 33 3% / 33	*Note: the percentages in the FDA review and prescribing information are up to 5 points higher for each study arm for the primary endpoint* • Blinding could be compromised by obviousness and frequency of adverse reactions. • Use of erythropoietin stimulating agents was excluded from telaprevir studies. • Level of treatment adherence unclear • Extensive inclusion/exclusion criteria found in study protocol. May impact application and results in general clinical setting. • Too few African-American and Hispanic patients to adequately assess response in these populations. Race and ethnic groups were self-reported and not mutually exclusive (e.g., Hispanic) • Discontinuation due to adverse reactions in TVR group high but overall discontinuation rates higher in PR group due to stopping rules: 7% T12PR24, 52% T12PR48, 8% T8PR24, 56% T8PR48, 79% PR • Subgroup analysis: T12PR performed better than PR in all subgroup analyses (sex, age, race, ethnicity, HCV subtype, baseline HCV, fibrosis status, BMI, baseline HCV RNA, diabetes history, geographic region; however, for cirrhosis and baseline HCV RNA <800K CI rate of SVR: differences not significant: ≈0.3 (CI ≈ 0.0 to 0.6) and ≈0.1 (CI ≈ –0.05 to 0.25). • Stopping rules to prevent continuing treatment in patients without adequate response applied: Patients receiving telaprevir with HCV RNA >1000 IU/mL at week 4 D/C telaprevir but continued PR. All patients with <2 $\log_{10}$ decrease from baseline in HCV RNA at week 12 D/C treatment. Patients with HCV RNA detectable at any time between weeks 24 and 40 D/C treatment. Stopping rules: 1. D/C TVR or PLA required for progressive grade 2 (moderate, diffuse, involving up to 50% of body), or grade 3 (severe, involving more

									than 50% of body or systemic changes) rash. 2. D/C TVR or PLA if RIB D/C due to anemia.
REALIZE									Fair
Zeuzem Centers in 17 countries Phase 3 Sep 2008–July 2010 RCT, stratified, PC, DB	1. T12PR48: T (750 mg q8h) plus P (180 µg per week) and R (1000 mg to 1200 mg qd) for 12 weeks, then PLA plus PR for 4 week, then PR for 32 weeks 2. lead-in T12PR48: PLA plus PR for 4 weeks, the T plus PR for 12 weeks, then PR for 32 weeks 3. PR48 (control): PLA plus PR for 16 weeks, then PR for 32 weeks Note: doses are the same for each drug in all arms.	Inclusion criteria: • aged 18–70 • chronic HCV genotype 1 • no SVR to one previous course of PR despite receiving 80% of intended dose • detectable HCV RNA • liver biopsy within 18 mo. of screenin Exclusion criteria: • absolute neutrophil count <1200 per ml^3, platelet count <90K per ml^3, hgb <12 g/dL women or <13 g/dL men • significant liver disease (e.g., cancer, decompensation) Patient characteristics: Age (mean): 51 yrs Male: 69% White: 93% Black: 5% Hispanic: 11% HCV RNA ≥800K IU per ml: 89% HCV genotype 1a: 45% HCV genotype 1b: 45% HCV genotype 1c: <1% HCV genotype unk: 10% Cirrhosis: 26% Bridging fibrosis: 22% Previous type of response: No response: 28% Partial: 19% Relapse: 53% Stratified by baseline viral load (HCV RNA <800K or ≥800K IU per mL) and type of previous response to treatment PR (no response, partial response, or	1. 266 2. 264 3. 132 modified ITT	Primary outcome assessed 24 weeks after end of treatment (i.e., week 48)	<u>Sustained virological response:</u> Previous relapse: 1. T12PR48: 83% (p<0.001) 2. lead-in T12PR48: 88% (p<0.001) 3. PR48: 24% No previous virologic response or partial response: 1. T12PR48: 41% (p<0.001) 2. lead-in T12PR48: 41% (p<0.001) 3. PR48: 9% Previous partial response: 1. T12PR48: 59% (p<0.001) 2. lead-in T12PR48: 54% (p<0.001) 3. PR48: 15% No previous virologic response: 1. T12PR48: 29% (p<0.001) 2. lead-in T12PR48: 33% (p<0.001) 3. PR48: 5% Overall: 1. T12PR48: 64% (p<0.001) 2. lead-in T12PR48: 66% (p<0.001) 3. PR48: 17%	59%/2 64%/2 32%/3 32%/3 44%/2 39%/3 24%/4 28%/4 47%/2 (CI: 37–57) 49%/2 (CI: 40–60)	Rash 1. T12PR48: 37% 2. Lead-in T12PR48: 36% 3. PR48: 19% Pruritus: 1. T12PR48: 52% 2. Lead-in T12PR48: 50% 3. PR48: 27% Anemia: 1. T12PR48: 30% 2. Lead-in T12PR48: 36% 3. PR48: 15% All-drug discontinuation due to adverse reaction: 1. T12PR48: 6% 2. Lead-in T12PR48: 4% 3. PR48: 3%	18% / 6 17% / 6 25% / 4 23% / 4 15% / 7 21% / 5 3% / 3 1% / 100	*Note:The percentages in FDA review and REALIZE supplement for each study arm for each subgroup for the primary endpoint are 1 or 2 points higher or lower and the SVR for null responders on PR48 zero.* • Blinding could be compromised by adverse reaction type. HCV RNA testing results unblinded after week 24. • Level of treatment adherence unclear • Extensive inclusion/exclusion criteria found in study protocol. May impact application and results in general clinical setting. • Too few African-American and Hispanic patients to adequately assess response in these populations. Race and ethnic groups were self-reported and not mutually exclusive (e.g., Hispanic) • Discontinuation due to adverse reactions in TVR group high but overall discontinuation rates higher in PR group due to stopping rules: 1. T12PR48: 38% 2. Lead-in T12PR48: 30% 3. PR: 62% • Guideline definitions of null responder and partial responder use an evaluation point of 24 weeks, whereas REALIZE uses 12 weeks. • Overall 73% of virologic failures and relapses due to emergence of variants with reduced sensitivity to TVR. Stopping rules: a. TVR stopped if HCV RNA >100 IU per mL at weeks 4, 6, and 8. All treatment D/C if patient had <2log_{10} decrease in HCV RNA at week 12 in the T12PR48 group and the control group or at week 16 in the lead-in group or in cases of detectable HCV RNA at week 24 or 36. (D/C TVR for stopping rule = treatment failure.)

		relapse)							b. D/C TVR required for progressing to grade 2 and for grade 3 rash but PR continued. D/C R, with or without P, if no improvement in rash within 7 days. c. If decrease or D/C RIB due to anemia and did not improve anemia, then d/c TVR.
ILLUMINATE									Fair
Sherman 74 centers Phase 3 Open label, randomized, noninferiority, stratified, DB for results of HCV RNA testing through week 24	1. T12PR24: T (750 mg q8h) plus P (180 µg per week) and R (1000 mg qd for <75 kg or 1200 mg qd for ≥75 mg qd) for 12 weeks, then PR for 12 weeks 2. T12 PR48: T plus PR for 12 weeks, then PR for 36 weeks Note: doses are the same for each drug in all arms.	Inclusion criteria: • aged 18–70 • chronic HCV genotype 1 • no previous treatment • liver biopsy Exclusion criteria: • HIV or HBV positive • absolute neutrophil count <1500 per ml^3, platelet count <90K per ml^3, hgb <12 g/dL women or <13 g/dL men • significant liver disease Characteristics of randomly assigned patients: Age (mean): 51 yrs Male: 62% White: 83% Black: 11% Hispanic: 9% HCV RNA ≥800K IU per ml: 78% HCV genotype 1a: 72% HCV genotype 1b: 28% HCV genotype unk: <1% Cirrhosis: 9% Bridging fibrosis: 13% Once randomized, stratified by HCV genotype subtype and black v. non-black	1. 162 2. 160 eRVR population	Primary outcomes assessed 24 weeks after end of treatment (i.e., week 48 or 72)	<u>difference in SVR between patients who had eRVR</u> 1. T12PR24: 92% 2. T12PR48: 88% RR 1.0	NS	Rash: 1. T12PR24: 37% 2. T12PR48: 39% Pruritus: 1. T12PR24: 59% 2. T12PR48: 52% Anemia: 1. T12PR24: 42% 2. T12PR48: 41% All-drug discontinuation due to adverse reactions: 1. T12PR24: 1% 2. T12PR48: 12%	NA NA NA	*Note: the percentages noninferiority CI in FDA review was –4.3 to +8.2% and SVR rate was 90%, rather than 88% for T12PR48* • Open-label • Level of treatment adherence unclear • Treatment unblinded. Only HCV RNA testing results DB through week 24 • Extensive inclusion/exclusion criteria found in study protocol. May impact application and results in general clinical setting. • Overall discontinuation rates after eRVR randomization: 1. T12PR24: 1% 2. T12PR48: 26% • Overall discontinuation rate prior to randomization: 18% • Randomization to stop PR treatment at week 24 or week 48 occurred at week 20 for patients with eRVR. • Stopping rule: TVR stopped in patients with HCV RNA >1000 IU/mL at week 4. All study drugs stopped in patients with virologic failure at week 12 or between weeks 24 and 36 (virologic failure = HCV RNA >1000 IU/mL at week 4, a decline from baseline by <2log$_{10}$ units in level of detectable HCV RNA at week 12, or a detectable HCV RNA level at any time between weeks 24 and 36.) • Noninferiority margin –10.5%. 80% power to rule out noninferiority if observed SVR rate was 90%

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Clinical Findings

The FDA reviewed six phase 2 studies and three phase 3 studies in making its determination for approval of TVR. Three phase 2 and three phase 3 studies have been published.

Phase 2 studies established that dosing TVR, in combination with PR, for more than 12 weeks held no advantages and that the treatment should include RIB to mitigate breakthrough and relapse rates. Researchers also initiated the exploration of response-guided therapy (RGT) in phase 2 studies and continued the evaluation in the phase 3 studies ADVANCE and ILLUMINATE.[3,4,6,9–11]

The ADVANCE and ILLUMINATE trials included adult treatment-naïve subjects with HCV-1, while the REALIZE phase 3 trial included adult subjects with HCV-1 who had been previously treated. The primary efficacy endpoint in all three trials was the proportion of patients achieving SVR. "Stopping rules" for discontinuing TVR or all treatment were applied to each study to prevent patients who did not have adequate response and patients with serious adverse events from continuing treatment. These patients counted as treatment failures.[4–6]

ADVANCE tested treatment duration: whether 8 or 12 weeks of TVR in combination with PR (T8PR and T12PR, respectively) was superior to 48 weeks of PR. Treatment arms had similar baseline characteristics and demographics. Both TVR-containing regimens were statistically superior to PR. The SVR rates for the T12PR (n=363), T8PR (n=364), and PR (n=361) modified ITT groups were 75%, 69%, and 44%, respectively, ($p<0.001$ comparing each TVR group with the PR group). The difference in responses were 31% (CI: 18–32) for T12PR versus PR and 25% for T8PR versus PR, giving NNTs of 3 and 4, respectively.[6]

About 60% of patients randomized to the TVR regimens achieved eRVR, compared to 8% in the PR group. Among patients achieving eRVR, 89% of T12PR and 83% of T8PR patients achieved SVR. These results indicated total treatment duration of 24 weeks would be sufficient for patients achieving eRVR, whereas a longer duration of PR would be preferred for patients who did not. Relapse occurred in 9%, 9%, and 28% of subjects receiving T8PR, T12PR, and PR, respectively.[6]

All patients with negative predictive factors (for sex, age, race, ethnicity, HCV subtype, baseline HCV RNA, fibrosis, BMI, diabetes) who took TVR had higher response rates than those randomized to PR treatment; however, differences in rate of SVR for cirrhosis and baseline HCV RNA <800,000 IU/mL did not reach significance: ≈0.3 (CI ≈ 0.0 to 0.6) and ≈0.1 (CI ≈ –0.05 to 0.25), respectively. SVR rates in historically difficult-to-treat subgroups (African-Americans, Hispanics, and cirrhotic patients) receiving TVR-containing regimens were about 30% above SVR rates for those taking PR alone. SVR rates for black patients were 62%, 58%, and 25% for T12PR, T8PR, and PR groups, respectively, and for bridging fibrosis or cirrhotic patients were 62%, 53%, and 33%, respectively. SVR rates for Hispanic patients were 74% and 39% for the T12PR and PR groups, respectively.[6]

ILLUMINATE was a supportive, open-label, non-inferiority trial that compared 12-weeks of TVR with 24- to 48-weeks of response guided therapy (RGT) in treatment-naïve subjects (n=540) who had achieved eRVR. Subjects achieving eRVR were randomized to receive 24 weeks or 48 weeks of therapy with PR in combination with TVR (T12PR24 or T12PR48, respectively). The predefined non-inferiority margin was –10.5%. Overall, 65% (352/540) patients achieved eRVR. Among subjects who achieved eRVR and were randomly assigned to a study group (n=322), 92% receiving T12PR24 compared to 88% receiving T12PR48 had SVR. Noninferiority was met with a two-sided CI of –2% to 11%. The SVR rate for cirrhotic subjects achieving eRVR and treated with 24-weeks of TVR-containing regimen was 67%, while the rate for those treated for 48 weeks was 92%. Although representation of cirrhotic patients was limited, cirrhotic patients may benefit from 48 weeks PR with 12-weeks of TVR.[3,4]

The REALIZE trial examined the efficacy and safety of TVR given for 12 weeks in combination with PR for 48 weeks in 662 previously treated HCV1 subjects who were relapsers (53%), partial responders (19%), or null responders (28%). The trial also evaluated whether a 4 week lead-in of PR prior to triple therapy would affect relapse and resistance. The baseline characteristics and demographics of the treatment arms were similar. Because this was a study of subjects previously treated with PR, the study had more cirrhotic subjects (26%) compared to trials with treatment-naïve patients. SVR rates for previous relapsers, partial responders, and null responders were higher for the TVR groups than the PR48 group ($p<0.001$ for all comparisons). Treatment outcomes were similar with or without lead-in.[3,5]

SVR

	T12PR48	Lead-in T12PR48	PR48
Relapsers	83% (121/145)	88% (124/141)	24% (16/68)
Partial responders	59% (29/49)	54% (26/48)	15% (4/27)
Null responders	29% (21/72)	33% (25/75)	5% (2/37)

Rates of relapse at 72 weeks were lower in the two TVR groups than the PR group among previous relapsers, partial responders, or null responders. However, the number of partial and null responders was small.

Relapse rates

	T12PR48	Lead-in T12PR48	PR48
Relapsers	7% (10/135)	7% (9/138)	65% (30/46)
Partial responders	21% (8/39)	25% (9/36)	(0)
Null responders	27% (8/30)	25% (9/36)	60% (3/5)

Overall, 73% of virologic failure and relapses were associated with treatment-emergent TVR-resistance.

Virologic failure rates (having virologic failure, i.e., ≥1 $\log_{10}$ increase in HCV RNA nadir during treatment or HCV RNA level >100 IU/mL when viral load had previously been <25 IU/mL during treatment, or meeting stopping rules)

	T12PR48	Lead-in T12PR48	PR48
Relapsers	1% (2/145)	1% (1/141)	26% (18/68)
Partial responders	18% (9/49)	19% (9/48)	70% (19/27)
Null responders	57% (41/72)	47% (35/75)	84% (31/37)

Among cirrhotic subjects, SVR was highest for relapsers (87% for TVR-containing regimens v. 13% for PR alone). SVR was low for null responders with or without TVR (14% v. 10%, respectively); however, the number of null responders was small.[3]

The ADVANCE trial established a treatment regimen including TVR for 12 weeks and PR for 24 weeks is superior to PR alone in treatment-naive patients who have achieved eRVR, while 48 weeks of PR with 12 weeks of TVR is recommended in patients not achieving eRVR. The ILLUMINATE trial established treating patients who had achieved eRVR with more than 24 weeks of PR in combination with TVR provided no advantage. The REALIZE trial supports the use of TVR-containing regimens in patients previously treated with PR alone. [3–6]

Internal and external validity concerns with phase 3 clinical trials included extensive inclusion and exclusion criteria, limited or no tracking of adherence, probability of compromised blinding, and whether similar efficacy and safety results can be achieved in a general clinical setting, as triple therapy requires strict and frequent monitoring of serum HCV RNA, adherence by clinicians to stopping rules and treatment regimens, management of an extensive list of probable and actual drug-drug interactions, and close monitoring for adverse reactions. The emergence of drug resistance, especially in patients who have had a prior non-response, are non-adherent to therapy, or are intolerant of optimal PR doses also is a concern.[12]

Despite these unknowns, triple therapy has overriding benefits, including improved SVR rates for patients as a whole, improved SVR rates for difficult-to-treat patients, shorter duration of therapy for treatment-naïve patients who achieve SVR, and a re-treatment option for patients who have failed previous therapy with PR.

DRUG SAFETY

Safety issues arising from clinical trials primarily focused on rash, pruritus, and anemia. Rash led to discontinuation of TVR and triple therapy in 6% and 1% of subjects, respectively, and anemia led to discontinuation of TVR and triple therapy in 4% and 1% of patients, respectively. In clinical trials, severe cutaneous adverse reactions were reported in <1% of subjects treated with TVR-containing regimens compared to 0% of subjects treated with PR alone. Whether the rates of severe rash, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Steven-Johnson Syndrome (SJS), seen in clinical trials represent the rates in a general treatment population is as yet unknown.[3]

Serious (REMS, Black Box Warnings, Contraindications):[1] Contraindications to peginterferon alfa and ribavirin also apply.
Triple therapy is contraindicated in women who are or may become pregnant and men whose female partners are pregnant. Because RIB is associated with significant teratogenic or embryocidal effects, female patients and female partners of childbearing age should use two effective contraceptive methods during and for 6 months following treatment. Female patients should use two effective non-hormonal contraceptives. Concomitant use of telaprevir with medications that have a narrow therapeutic index and are highly dependent on CYP3A4 is contraindicated. Concomitant use of telaprevir with medications that strongly induce CYP3A4 and may result in reduced efficacy of telaprevir is contraindicated. Serious adverse reactions requiring discontinuation of telaprevir include: (1) skin reactions, including DRESS and SJS; (2) severe rash or if systemic symptoms develop from rash; (3) anemia unresolved by RIB dose reduction. telaprevir is not recommended in moderate or severe hepatic impairment or with decompensated liver disease. telaprevir use in monotherapy is contraindicated, and its dose must not be reduced or be restarted if discontinued. During clinical trials, severe cutaneous adverse reactions were reported in <1% of subjects treated with TVR-containing regimens compared to 0% of subjects treated with PR alone. Three cases (1 possible, 1 probable, 1 unlikely) of SJS and 11 cases (1 definite, 2 probable, 8 possible) of DRESS occurred.

Monitoring:[1,3] Monthly pregnancy tests; hemoglobin before and at least every 4 weeks during TVR therapy; HCV-RNA levels at weeks 4 and 12 and as clinically indicated; hematological and blood chemistry evaluations at weeks 2, 4, 8, and 12 or as clinically indicated thereafter.[1]

Tolerability:[1,3] During phase 2 and 3 studies, 8% to 14% of patients treated with TVR-containing regimens discontinued TVR due to adverse reactions compared to about 3% of those treated with PR. The most frequent reactions leading to discontinuation of TVR were rash, pruritus, anemia, fatigue, nausea, and vomiting (see Adverse Reactions table below). Three percent of patients receiving TVR had serious adverse reactions compared to none of the patients receiving PR. The most frequent serious adverse reactions for patients receiving TVR were skin reactions (rash and pruritus) and anemia. Rash led to discontinuation of TVR and triple therapy in 6% and 1% of subjects, respectively, and anemia led to discontinuation of TVR and triple therapy in 4% and 1% of patients, respectively. Incidence of ano-rectal discomfort (e.g., hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) combined were 29% for patients receiving TVR versus 7% for those receiving PR. Most of these reactions were mild or moderate and lead to only 1% of patients discontinuing therapy. Uric acid levels were elevated in 73% of patients receiving TVR compared to 29% of patients receiving PR. However, less than 1% of cases resulted in gout or gouty arthritis, and no patients discontinued therapy for this reason.

Pregnancy/Lactation:[1,3] Although the pregnancy category of TVR alone is B, the pregnancy category for combination therapy is X, since RIB has caused birth defects or fetal deaths in all animal species studied and PEG is abortifacient in animals. Nursing must be discontinued prior to initiation of treatment, because of the potential for adverse reactions in nursing infants.

Unanswered safety questions:[3] A concern is the management of serious skin reactions in general clinical setting, as mismanagement could lead to death. There's also concern whether the clinical trials accurately predict the incidence of SJS and DRESS.

Dose Index (efficacy/toxic):[1,3] *The* effective dose is 750 mg every 8 hours. The highest documented dose of TVR administered alone is 1875 mg every 8 hours for four days in healthy human subjects. Adverse events reported more frequently at that dose in comparison to 750 mg every 8 hours were nausea, headache, diarrhea, decreased appetite, dysgeusia, and vomiting. Also, higher dose exposure was significantly associated with increased risk of anemia or hemoglobin toxicity (hgb <10g/dL or a decrease of 3.5 g/dL from baseline).

Several other unanswered questions remain with regard to treatment and safety, including:
How do non-Caucasian, cirrhotic, liver-transplant, or HIV or HBV co-infected patients respond to TVR therapy, as representation of historically difficult-to-treat subjects was limited in all trials?
What is the dosing for pediatric patients?
What factors, such as genetics, are associated with severe skin reactions?
Would patients previously failed treatment with a TVR-containing regimen respond to a repeat course of therapy?
What is the long-term clinical impact of emergence or persistence of TVR-associated resistance amino acid substitutions?
What is the impact of TVR exposure or treatment failure on the efficacy of other HCV NS3/4 protease inhibitors, such as boceprevir? Researchers have demonstrated NS3 amino acid substitutions (V36, T54, R155, A156, or D168) detected in TVR-treated subjects who did not achieve SVR in clinical trials reduces the anti-HCV activity of boceprevir and other NS3/4 protease inhibitors.[3]
What anti-HCV activity does TVR have against non-genotype 1 HCVs?[3]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexicomp, USP Online LASA Finder, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexicomp	USP Online	ISMP	Clinical Judgment
LA/SA for telaprevir (generic)	None	None	None	None
LA/SA for Telaprevir™(brand)	None	None	None	None

ADVERSE REACTIONS[1]

Table 4: Clinical Adverse Drug Reactions Reported with at Least 5% Higher Frequency Among Subjects Receiving INCIVEK

	INCIVEK, peginterferon alfa, and ribavirin Combination Treatment N=1797	Peginterferon alfa and ribavirin N=493
Rash*	56%	34%
Fatigue	56%	50%
Pruritus	47%	28%
Nausea	39%	28%
Anemia*	36%	17%
Diarrhea	26%	17%
Vomiting	13%	8%
Hemorrhoids	12%	3%
Anorectal discomfort	11%	3%
Dysgeusia	10%	3%
Anal pruritus	6%	1%

*Rash and anemia based on SSC (Special Search Category) grouped terms.

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose
375 mg	Tablet	Oral	750 mg three times daily (7-9 hour apart)	None	None for mild hepatic impairment. Not recommended for moderate or severe hepatic impairment (Child-Pugh B or C, score ≥7)	Safety and effectiveness not established	Response to therapy in patients ≥ 65 years old is uncertain; therefore, caution should be exercised

OTHER DOSING CONSIDERATIONS:

- Administer with food (not low fat), otherwise exposure may be inadequate
- Duration of therapy for patients achieving eRVR is 12 weeks of TVR and 24 weeks of PR. Patients without eRVR and prior partial and null responders should receive 12 weeks of TVR plus 48 weeks of PR. Treatment-naïve patients who have cirrhosis and eRVR may benefit from 48 weeks of PR. (Note: a high proportion of previous null responders, particularly those with cirrhosis, did not achieve SVR and had TVR-resistance substitutions emerge.)
- The dose of telaprevir must not be reduced or interrupted.
- Application of stopping rules are recommended: If HCV RNA at week 4 or 12 is ≥1000 IU/mL, d/ctelaprevir and PR (telaprevir treatment complete at 12 weeks). If HCV RNA is detectable at week 24, d/c PR.
- The safety and efficacy of telaprevir have not been established in patients co-infected with HCV/HIV or HCV/HBV and in solid organ transplant patients.
- See prescribing information for PEG and RIB for other dosing considerations.

PHARMACOKINETICS[1,3]

Parameter	Result
Oral Bioavailability	Varies with species (from <22% in rabbits to 70–95% in fed dogs)*
Protein Binding	59% to 76%
Elimination	82% in the feces, 9% in exhaled air, 1% in urine
Half-Life	9 to 11 hours at steady state
Metabolism	CYP3A4 (major)

*Food markedly affects exposure to TVR, with up to four-fold increase in exposure when administered with standard test breakfast. Higher fat content increases exposure.

PHARMACOGENETICS[1]

Retrospective studies indicate triple therapy increased SVR rates regardless of genotype in treatment-naïve and treatment-experienced patients. However, these results should be viewed cautiously, because the sample size was small and the substudy populations may not represent the full trial populations.

ALLERGIES/INTERACTIONS[1]

Drug-Drug:

TVR is a substrate and strong inhibitor of CYP3A4 and a substrate and inhibitor of P-glycoprotein.

Drugs contraindicated (adverse event): alfuzosin (hypotension or cardiac arrhythmia), rifampin (reduced TVR plasma concentration), ergot derivatives (acute ergot toxicity), St. John's wort (reduced TVR plasma concentration), atorvastatin or lovastatin or simvastatin (myopathy), pimozide (cardiac arrhythmias), sildenafil or tadalafil dosed for pulmonary arterial hypertension (PDE5 inhibitor-associated adverse events), oral midazolam or triazolam (increased sedation or respiratory depression), and cisapride (cardiac arrhythmias).

Dozens of other drug interactions with TVR are predicted or have been confirmed via studies. Several of these drugs require dose adjustments or clinical monitoring when used concomitantly with TVR.

Food-Drug: No food-drug interactions have been reported.[1]

APPENDIX 1
Suggested PA Criteria

Hepatitis C Oral Protease Inhibitors/Triple Therapy

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #5	**No:** Pass to RPh, Deny For Appropriateness
5. Does the patient have a pre-treatment viral load (since diagnosis)?	**Yes:** Go to #6	**No:** Pass to RPh; Deny For Appropriateness; Recommend viral load
6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. Has prior authorization been granted for peginterferon alfa-2a or -2b and ribavirin or does patient meet prior authorization criteria for pegylated interferon-alfa?	**Yes**: Go to #8	**No**: Pass to RPh; Deny for appropriateness
8. Is the request for continuation of therapy? (Patient has been on triple therapy with a oral antiviral agent in preceding 6 weeks)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #9
9. Has the patient previously been treated with boceprevir or telaprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #10
10. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 6 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #11 (If dose is different pass to RPh for appropriateness)
11. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 10 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Pass to RPh; Deny for appropriateness

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis who has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
***TREATMENT FUTILITY RULES** Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks) Week 24: Detectable Discontinue peginterferon and ribavirin. If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued		

Continuation of Therapy- Boceprevir		
1.Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8,12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.		

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Month/Year of Review: November 2011
Generic Name: Boceprevir
Brand Name: Victrelis™
PDL Class: Hepatitis C Antivirals

End date of literature search: 4th Quarter 2011
Manufacturer: Merck & Co., Inc.
Dossier received: No
Comparator Therapies: peginterferon alfa-2b plus ribavirin (PR) alone

FDA Approved Indications:[1] Boceprevir is indicated for treating chronic hepatitis C (CHC) genotype 1 infection, only in combination with peginterferon alfa and ribavirin (PR), in patients >18 years of age with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. The following should be considered when initiating therapy with boceprevir:
• Boceprevir efficacy has not been studied in patients previously failing therapy with a treatment regimen including boceprevir or other protease inhibitors for the treatment of hepatitis C virus.
• At this time, there are currently no published trials that evaluated boceprevir in combination with PR in patients with a prior null response (<2-$\log_{10}$ HCV-RNA decline by treatment week 12) to PR. The current clinical studies included subjects who were poorly interferon responsive. Subjects with <0.5-log10 HCV-RNA decline in viral load at treatment week 4 with PR alone are predicted to have a null response to PR therapy.
• Poorly interferon responsive (as determined at treatment week 4) patients treated with boceprevir in combination with PR have a lower likelihood of achieving a sustained virologic response (SVR), and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to PR.

Summary: American Association for the Study of Liver Diseases (AASLD) guidelines recommend triple therapy with boceprevir (BOC) in combination with PR as a first-line treatment for CHC[2]. Evidence for use of triple therapy comes from two phase 3 studies[3]. Moderate level evidence shows dosing BOC in combination with PR improved SVR rates in treatment-naïve[4] and in treatment-experienced patients[5], specifically partial responders and relapsers. However, several unresolved questions remain with regard to optimal treatment duration in cirrhotic patients, null responders, late responders, and black patients. In addition, studies did not directly compare response-guided therapy to fixed-duration therapy.

SPRINT-2 randomized 1099 subjects 1:1:1 and tested whether 24 weeks or 44 weeks of BOC plus PR (Group 2 and Group 3, respectively) was superior to 44 weeks of PR alone (Group1). Each treatment regimen was preceded by 4 weeks of PR therapy (i.e., lead-in). Groups 1 and 3 ended

treatment at week 48, Group 2 early responders ended treatment at week 28, while Group 2 late responders received an additional 20 weeks of PR and ended treatment at week 48. For the combined cohorts and for the black and non-black cohorts, BOC-containing regimens were statistically superior to PR. The absolute risk reductions (ARR) in SVR rates for the combined cohort were 25% for Group 2 v. 1 ($p<0.001$) and 28% for Group 3 v. 1 ($p<0.001$), giving NNTs of 4 for each comparison, respectively.[4] SPRINT-2 researchers indicated that a total treatment duration of 28 weeks would be sufficient for early responders, while 48 weeks of therapy (4 weeks of lead-in, 24 weeks of triple therapy, and 20 weeks of PR alone) would be preferred for late responders. However, the FDA recommended 4 weeks of lead-in, 32 weeks of triple therapy, and 12 weeks of PR for late responders based on a reanalysis of the SVR rates of Groups 2 and 3 and a subgroup analysis of early and late responders.

RESPOND-2 randomized 403 prior partial responders and relapsers 1:2:2 and tested whether 32 weeks or 44 weeks of BOC plus PR (Group 2 and Group 3, respectively) was superior to 44 weeks PR alone (48 weeks including lead-in). Groups 1 and 3 ended treatment at week 48. Group 2 early responders ended treatment at week 36, while Group 2 late responders received an additional 12 weeks of PR and ended treatment at week 48. Both BOC-containing regimens were statistically superior to PR. The ARR for SVR rates were 38% for Group 2 v. 1 ($p<0.001$) and 45% for Group 3 v. 1 ($p<0.001$), giving NNTs of 3 and 2, respectively.[5] Even though null responders were excluded from this trial, FDA reviewers recommended approval of triple therapy for null responders based on post-hoc analysis of treatment-naïve patients from SPRINT-2 who were identified as null responders by HCV level measured at treatment week 4 with a low cut-off: ≤ 0.5 $\log_{10}$ decline in HCV RNA. Patients who were null responders became eligible to enter a subsequent trial (the PROVIDE trial) and is ongoing. Post-hoc analysis established a 44-week triple therapy regimen for null responders as well as for cirrhotic patients. AASLD guidelines advise caution in using BOC in null responders.

Data establishes the superiority of BOC-containing regimens over PR alone, in general, despite several internal and external validity concerns leading to "fair" quality assessment ratings for phase 3 studies. Also, questions are outstanding with regard to dosing and response in treatment-naïve late responders, treatment-experienced null responders, and special populations and with regard to managing therapy in a general clinical setting and CHC population, given the careful monitoring for response, safety, and treatment adherence required for therapy.

The incidence of adverse reactions with triple therapy, and even for PR alone, are quite high and largely driven by the rates of anemia (45–50%), neutropenia (14–25%), nausea (43–46%), dysgeusia (35–44%), and diarrhea (24–25%). There was an absolute risk increase for developing anemia of 20% in SPRINT-2 for Groups 2 and 3 compared to the control group and an absolute risk increase of 23% and 26% in Respond-2 for Groups 2 and 3, respectively. Increased rates of anemia requiring use of an erythropoiesis stimulating agent (ESA) or transfusion is the greatest safety concern. In addition, treatment is complicated requiring patient adherence and timely laboratory monitoring to guide therapy. Triple therapy also is very expensive necessitating judicious use of these agents in patients.

PDL Placement Recommendation:

- Recommend BOC require prior authorization to limit its use to treatment in genotype 1 HCV with clinical, dose, and duration limits (Appendix 1).

- Consider other considerations such as duration of therapy, complexity of dosing regimen, pill burden, side effect profile, and evidence in previous null responders when evaluating BOC and TVR.

- Due to high cost of treatment and lack of comparative effectiveness evidence, recommend evaluating OHA costs for both BOC and TVR for consideration of OHA management.

BACKGROUND/CURRENT LANDSCAPE

CHC Treatment response is defined by surrogate biochemical, histological, and virological parameters, rather than clinical endpoints such as liver disease and death, because the natural history of CHC evolves over decades.[6] Short-term outcomes include normalization of serum ALT levels, 2 point improvement in necroinflammatory score with no worsening in fibrosis score, and clearance of HCV RNA from serum as measured by PCR.[6]

Virological parameters are divided into the following: [6–9]

- sustained virological response (SVR): the absence of HCV RNA from serum by PCR 24 weeks after discontinuing therapy;
- end-of-treatment response (ETR): undetectable virus at the end of either a 24-week or 48-week course of therapy;
- rapid virological response (RVR): undetectable HCV RNA at week 4 of treatment (lower limit of detection 50 IU/mL by PCR);
- extended rapid virological response (eRVR): undetectable HCV RNA at weeks 4 and 12;
- early virological response (EVR): a ≥2 log reduction in or complete absence of serum HCV RNA at week 12 of therapy compared with the baseline level;
- virological breakthrough: the reappearance of HCV RNA while still on therapy;
- virological relapse: the reappearance of HCV RNA in serum following treatment discontinuation and documented ETR;
- null responders: patients who fail to suppress serum HCV RNA by at least 2 logs after 24 weeks of therapy;
- early responder: undetectable HCV RNA at week 8 and 24 or weeks 8 through 24 of therapy (SPRINT-2 and RESPOND-2 trials);
- late responder: detectable HCV RNA at week 8 but undetectable HCV RNA at week 24 (SPRINT-2 and RESPOND-2 trials);
- partial responders: patients whose HCV RNA levels decreased by ≥2 $\log_{10}$ IU/mL at week 12 but never became undetectable; and
- non-responders: patients who fail to clear HCV RNA after 24 weeks of therapy.

Areas of focus for therapeutic development have been on increasing the SVR rates in patients with HCV-1 infection who have a high viral load, African ancestry, or failed previous therapy and, because of the side effects association with PR treatment, decreasing the duration of therapy.[6, 7]

The molecular characterization of HCV and its life-cycle has led to the development of directly acting antiviral agents (DAAs), which target enzymes essential for HCV replication.[7]Two NS3/4A serine protease inhibitors, telaprevir and boceprevir, were recently approved by the Food and Drug Administration (FDA).[10]

Since the introduction of DAAs, AASLD guidelines from the have been updated and state: [2]

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. (Class 1, Level A)
2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. (Class 1, Level A).

AASLD dosing guidelines are as follows:
3. The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (Class 1, Level A).
4. Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B).
8. Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B).
10. Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1, Level A).
12. Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C).

AASLD recommendations with regard to stopping treatment are as follows:
5. Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (Class 2a, Level B).
13. Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12

should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).
15. Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (Class2a, Level A).
16. Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if biological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed (Class 1,Level A).
17. Patients who fail to have a biological response, who experience biological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (Class 2a, Level C).

CLINICAL PHARMACOLOGY: [1]

BOC is a reversible, DAA against HCV. BOC works by selectively inhibiting the HCV NS3/4A serine protease, which is essential for the production of nonstructural proteins NS4A, NS4B, NS5A, and NS5B and for viral replication. Several NS3 amino acid substitutions confer resistance to BOC. Variants emerging most frequently in patients who did not achieve SVR include V36M, T54S, R155K for HCV genotype 1a and T54A, T54S, V55A, A156S, I/V170A for genotype 1b.

COMPARATIVE CLINICAL EFFICACY[4, 5, 10]

Relevant Endpoints: 1) Sustained virological response (SVR)
2) Relapse rate
3) Withdrawals due to adverse effects
4) Anemia

Primary Study Endpoint: 1) Sustained virological response

Evidence Table

Ref./Study Design[1]	Drug Regimens	Patient Population	N	Duration (weeks)	Efficacy Results[2] (CI, p-values)	ARR/NNT (CI, p-values)[3]	Safety Results^ (CI, p-values)	ARR/ NNH[4]	Quality Rating/Comments
SPRINT-2									Fair
Poordad (About 200 centers planned) Phase 3 Aug 2008 to Ja 2009 RCT, PC, DB for BOC/PLA only, stratified	1. Group 1 (control): lead-in with peginterferon alfa-2b (P) (1.5 µg/kg sc per week) plus ribavirin (R) (600–1400 mg daily, divided) for 4 weeks, then placebo (PLA) plus PR for 44 weeks 2. Group 2 (RGT): lead-in with PR for 4 weeks, then boceprevir (B) (800 mg tid) plus PR for 24 weeks. If detectable HCV RNA at any point weeks 8–23 but not week 24 (late response), then PR plus PLA for 20 weeks more 3. Group 3 (fixed-duration therapy): lead-in with PR for 4 weeks, then BPR for 44 weeks Note: doses are the same for each drug in all arms.	Inclusion criteria: • age >18 • weight 40–125 kg • chronic infection with HCV-1 • no previous treatment • HCV RNA level ≥10K IU/mL Exclusion criteria: • HIV or HBV positive • liver disease of other cause • decompensated cirrhosis • renal insufficiency • pregnant or breast feeding • active cancer Patient characteristics: Age (mean): 49 yrs Male: 60% White: 82% Black: 14% Weight (mean): 81 kg HCV RNA ≥800K IU per ml: 85% HCV genotype 1a: 64% HCV genotype 1b: 33% HCV genotype unk: 3% Metavir fibrosis score 3 or 4: 9% Stratified by baseline HCV RN level (≤400 K v. >400K IU/mL) and HCV-1 genotype 1a v. 1b	1. 363 2. 368 3. 366 Modified ITT	Treatment duration 28 or 48 weeks. Primary outcome assessed week 72 (24 weeks following end of therapy for Groups 1 and 3 and Group 2 with detectable HCV RNA week 8–24 (late responders) and 44 weeks following therapy for Group 2 with undetectable HCV RNA weeks8–24 (early responders)	<u>proportion of treatment-naïve patients who had SVR</u> 1. Group 1: 38% 2. Group 2: 63% (p<0.001) 3. Group 3: 66% (p<0.001) Black cohort: 1. Group 1: 23% 2. Group 2: 42% (p=0.04) 3. Group 3: 53% (p=0.004) Non-black cohort: 1. Group 1: 40% 2. Group 2: 67% (p<0.001) 3. Group 3: 68% (p<0.001) Other: % patients with SVR who had undetectable HCV RNA weeks 8–24 (early responders): 1. Group 1: 93% (n=43) 2. Group 2: 96% (n=162) 3. Group 3: 96% (n=161) % patients with SVR who had detectable HCV RNA weeks 8–24 (late responders): 1. Group 1: 66% (n=131) 2. Group 2: 72% (n=82)	 25% / 4 28% / 4 19% / 5 30% / 3 27%/4 28%/4 NS NS NS NS	Anemia 1. Group 1: 29% 2. Group 2: 49% (p<0.001) 3. Group 3: 49% (p<0.001) Discontinuation due to adverse reaction: 1. Group 1: 16% 2. Group 2: 12% 3. Group 3: 16%	 20% / 5 20% / 5	• Blinding could be compromised because PR open label and treatment duration for group 2 patients with undetectable HCV RNA weeks 8–24 stop therapy at week 28 • Protocol says adherence to be checked, but adherence not reported in publication • Unable to ascertain appropriate dosing duration for early v. late responders • Subgroup analysis (race, sex, viral load, age, weight, BMI, platelet count, fibrosis, steatosis, cirrhotics, HCV genotype, ALT, country) showed the numerical odds of SVR response was greater, across all subgroups, for either group 2 or 3 than group 1, except for cirrhotic patients. Additionally, a statistically significant difference was not seen for viral load >800K IU/mL, BMI ≤25 kg/m^2, platelet count >150K–200K IU/µL, fibrosis score 3 or 4 for group 2 v. 1; and age ≤40, platelets <200K/µL, and fibrosis score 3 or 4 for group 3 v. 1. • Stopping rules: a. d/c treatment for all patients with detectable HCV RNA at week 24 b. If virologic breakthrough or incomplete virologic response and rebound, d/c BOC but continue PR for up to 48 weeks • Discontinuation due to stopping rule 1a above: 1. Group 1: 30% 2. Group 2: 9% 3. Group 3: 10% • Carried forward HCV RNA measurement at 12 weeks of follow-up for patients missing HCV RNA measurement at the end of follow-up • Extensive inclusion/exclusion criteria found in study protocol. May impact application and results in general clinical setting. • Addition of BOC to therapy significantly

					3. Group 3: 75% (n=73) *By FDA analysis excluding 14 patients from Group 2:* *2. Group 2: 66% (n=68)* *3. Group 3: 75% (n=73)* Relapse rate: 1. Group 1: 22% 2. Group 2: 9% 3. Group 3: 9%	 13% / 8 13% / 8			increased the incidence of anemia requiring erythropoietin administration or transfusion. Erythropoietin, groups 1, 2, and 3: 24%, 43% (p<0.001), 43% (p<0.001) Transfusion, groups 1, 2, and 3: 1%, 3% (p=0.02), 2% (NS) No significant difference in the rate of serious adverse reactions between groups 1, 2, and 3: 9%, 11%, 12% • Overall BOC-resistance-associate variants: 17% group 2; 15% group 3 • Used step-down hypothesis testing: Group 3 first compared with group 1. If p≤0.05, the superiority of fixed duration therapy over standard therapy supported, and group 2 then compared with group 1. If p≤0.05, the superiority of RGT over standard therapy established.
RESPOND-2									Fair
Bacon 80 centers Phase 3 Aug–Nov 2008 RCT, PC, DB for BOC, stratified	1. Group 1 (control): lead-in with P (1.5 µg/kg per week) plus R (600–1400 mg daily, divided) for 4 weeks, then PLA plus PR for 44 weeks 2. Group 2 (RGT): lead-in PR for 4 weeks, then B (800 mg tid) plus PR for 32 weeks. If detectable HCV RNA at 8 weeks (but undetectable at 12 weeks), then PR 12 weeks more 3. Group 3:	Inclusion criteria: • previously treated for HCV-1 • demonstrated responsiveness to PR (12 weeks min. therapy) •partial responder or relapser Exclusion criteria: • HBV or HIV positive • absolute neutrophil count <1500 per ml^3 for non-blacks <1200 per ml^3 for blacks, platelet count <100K per ml^3, hgb <12 g/dL women or <13 g/dL men • other causes of significant liver disease • decompensated liver disease •uncontrolled diabetes • severe psychiatric disorder • active substance abuse Patient characteristics: Age (mean): 53 yrs Male: 67% White: 85% Black: 12%	1. 80 2. 162 3. 161 modified ITT	Treatment duration 36 or 48 weeks. Primary outcome assessed at week 72 (24 weeks after the end of treatment for groups 1 and 2 and 24 or 36 weeks after the end of treatment for group 2)	<u>Proportion of patients who had SVR</u> 1. Group 1: 21% 2. Group 2: 59% 3. Group 3: 66% Other: Prior relapse: 1. Group 1: 29% 2. Group 2: 69% 3. Group 3: 75% Relapse: Group 1: 32% Group 2: 15% Group 3: 12%	 38% / 3 (CI: 26 to 49, p<0.001) 45% / 2 (CI:34 to 57, p<0.001) 40% / 3 46% / 2 17% / 6 20% / 5	<u>Anemia</u> 1. Group 1: 20% 2. Group 2: 43% (p<0.001) 3. Group 3: 46% (p<0.001) Discontinuation due to adverse reaction: 1. Group 1: 2% 2. Group 2: 8% 3.Group 3: 12%	23% / 4 26% / 4 6% / 17 10% / 10	*Notes: The percentage for group 1 SVR rate in FDA review was 23% and % relapse for Group 1 28% and Group 2 14%.Bacon et al. use the term "non-response" for what the FDA and guidelines define as partial response, so partial response substituted for non-response.* • Blinding compromised because PR open label and group 2 patients with undetectable HCV RNA at weeks 8 and 12 stop therapy at week 36 • Protocol says adherence to be checked, but adherence not reported in publication • Groups 2 and 3 had greater percent of patients with high viral load (>800K IU/mL) than group 1 (control): 91%, 88%, 81%, respectively (p=0.04 group 2 v. group 1) • Overall, treatment discontinuation: 1. Group 1: 69% 2. Group 2: 32% 3. Group 3: 34% • Stopping rules:

	lead-in with PR for 4 weeks, then BPR for 44 weeks Note: doses are the same for each drug in all arms.	Weight (mean): 85 kg HCV RNA ≥800K IU per ml: 88% HCV genotype 1a: 59% HCV genotype 1b: 40% HCV genotype unk: 1% Metavir fibrosis score 3 or 4: 19% Cirrhosis: 12% Previous type of response: Prior partial response: 36% Prior relapse: 64% Stratified by partial response or relapse and HCV subtype 1a or 1b (unknown genotype randomly assigned)							a. Failure to achieve an undetectable HCV RNA level at week 12 resulted in d/c of all treatment b. If a patient had virologic breakthrough or an incomplete virologic response and rebound while receiving therapy, BOC could by d/c but PR continued for up to 48 weeks. • Extensive inclusion/exclusion criteria found in study protocol. May impact application and results in general clinical setting. • Too few African-American patients to adequately assess response in this population. Race and ethnic groups were self-reported. • Subgroup analysis: the numerical odds of SVR response was greater, across all subgroups, for either group 2 or 3 than group 1, although statistical significance was not reached for weight <75 kg, platelet count ≤200/µL, and fibrosis score 3 or 4 for group 2 v. group 1. Not enough cirrhotic patients to adequately perform subgroup analysis in cirrhotic patients. • Addition of BOC to therapy significantly increased the incidence of anemia requiring erythropoietin administration or transfusion. Erythropoietin, groups 1, 2, and 3: 21%, 41% (p=0.003), 46% (p<0.001) Transfusion, groups 1, 2, and 3: 0%, 2% (NS), 9% (p=0.006) Incidence of serious adverse reaction significantly greater for group 3: 5%, 10% (NS), 14% (p=0.03) for groups 1, 2, and 3, respectively. • Carried forward HCV RNA measurement at 12 weeks of follow-up for 13 patients missing HCV RNA measurement at the end of follow-up

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Clinical Findings

The FDA primarily based their efficacy and safety review of BOC on two phase 3 studies (SPRINT-2 and RESPOND-2), both of which have been published.[5], [4] an open-label phase 2 study (SPRINT-1) also has been published.[11] Both phase 3 studies compared response-guided therapy (Group 2) and fixed-duration therapy (Group 3) to PR alone (Group 1). SPRINT-2 included adult treatment-naïve subjects with HCV-1, while the RESPOND-2 included adult subjects with HCV-1 who had been previously treated, specifically partial responders and relapsers. The SPRINT-2 trial also had two cohorts, one black and one non-black. The primary efficacy endpoint in both trials was the proportion of patients achieving SVR. "Stopping rules" for discontinuing BOC or all treatment were applied to each study to prevent patients who did not have adequate response from continuing treatment. All treatment regimens included a four-week "lead-in" period of dosing with PR alone, which was shown in the phase 2 study to confer a numerical advantage in SVR rates. Assume the four-week lead-in for all treatment regimens below, when total duration not given.[4, 5, 11, and 12]

SPRINT-2 randomized 1099 subjects 1:1:1 and tested whether 24 weeks or 44 weeks of BOC plus PR (Group 2 and Group 3, respectively) was superior to 44 weeks PR alone (48 weeks including lead-in). Groups 1 and 3 ended treatment at week 48. Group 2 early responders ended treatment at week 28, while Group 2 late responders received an additional 20 weeks of PR and ended treatment at week 48. Treatment arms had similar baseline characteristics and demographics. For the combined cohorts and for the black and non-black cohorts, BOC-containing regimens were statistically superior to PR. The SVR rates for Groups 1, 2, and 3, modified intent to treat, were 38%, 63%, and 66%, respectively ($p<0.001$ comparing each BOC group with the PR group). The differences in responses were 25% for Group 2 v. 1 and 28% for Group 3 v. 1, giving NNTs of 4 and 4, respectively.[4]

For the black cohort, SVR rates were 23%, 42%, and 53% for Groups 1, 2, and 3, respectively, and for the non-black cohort 40%, 67%, and 69%, respectively. Post hoc analysis suggests most of the 11 percentage point difference between Groups 2 and 3 of the black cohort may be attributed to imbalances in the number of subjects discontinuing therapy during the PR lead-in phase and poor response from cirrhotic subjects.[4, 10]

About 44% of patients randomized to the BOC regimens were early responders, compared to 12% in the PR group. Among patients with an early response, 96% of Group 2 and 3 subjects and 93% of Group 1 subjects achieved SVR. SPRINT-2 researchers indicated a total treatment duration of 28 weeks would be sufficient for early responders, while 48 weeks of therapy (4 weeks of lead-in, 24 weeks of triple therapy, and 20 weeks of PR alone) would be preferred for late responders. However, the FDA recommended a total treatment duration of 48 weeks (4 weeks of lead-in, 32 weeks of triple therapy, 12 weeks of PR) for late responders based on a reanalysis of the SVR rates of Groups 2 and 3 and a subgroup analysis of early and late responders. While SPRINT-2 trial researchers, identified a 3% difference in SVR rate between Groups 2 and 3 late responders, the FDA calculated a 9% difference upon excluding 14 subjects its researchers believed were likely early responders, rather than late responders. Furthermore, the FDA noted that (1) the difference between Groups 2 and 3 primarily was due to virologic breakthrough shortly after stopping BOC and (2) RESPOND-2 trial's treatment-experienced patients had received a longer duration of BOC therapy and had fewer virologic breakthroughs

after end of BOC therapy (the FDA reasoned SPRINT-2's late responders were similar to treatment-experienced patients when one looks at interferon responsiveness week 4). Therefore, a longer duration of triple therapy was warranted for late responders.[4, 12]

Subgroup analysis positive and negative predictive factors for SVR (race, sex, viral load, age, weight, BMI, platelet count, fibrosis, steatosis, cirrhotics, HCV genotype, ALT, country) showed the numerical odds of SVR response was greater, across all subgroups, for either group 2 or 3 than group 1, except for cirrhotic patients. However, the number of cirrhotic patients in each group was small (n=13, 16, and 24 for Groups 1, 2, and 3, respectively). Additionally, a statistically significant difference was not seen for viral load >800K IU/mL, BMI ≤25 kg/m^2, platelet count >150K–200K IU/µL, fibrosis score 3 or 4 for Group 2 v. 1; and age ≤40, platelets >200K/µL, and fibrosis score 3 or 4 for Group 3 v. 1.[4,12]

RESPOND-2 randomized 403 prior partial responders and relapsers 1:2:2 and tested whether 32 weeks or 44 weeks of BOC plus PR (Group 2 and Group 3, respectively) was superior to 44 weeks PR alone (48 weeks including lead-in). Groups 1 and 3 ended treatment at week 48. Group 2 early responders ended treatment at week 36, while Group 2 late responders received an additional 12 weeks of PR and ended treatment at week 48. Treatment arms had similar baseline characteristics, except that Groups 2 and 3 had greater percent of patients with high viral load (>800K IU/mL) than Group 1: 91%, 88%, and 81%, respectively (p=0.04 group 2 v. group 1). Both BOC-containing regimens were statistically superior to PR. The SVR rates for Groups 1, 2, and 3, modified intent to treat, were 21%, 59%, and 66%, respectively. The difference in responses were 38% (CI: 26 to 49, p<0.001) for Group 2 v. 1 and 45% (CI: 34 to 57, p<0.001) for Group 3 v. 1, giving NNTs of 3 and 2, respectively.[5]

RESPOND-2 excluded prior null responders from the trial because, according to the FDA, "the phase 2 trial in treatment-experienced patients was not interpretable."[12] Even though null responders had been excluded, FDA reviewers recommended approval of triple therapy for null responders based on post-hoc analysis of treatment-naïve patients from SPRINT-2 who were identified as likely null responders by HCV level measured at treatment week 4 with a low cut-off: ≤0.5 $\log_{10}$ decline in HCV RNA. Eighty-eight percent of subjects meeting this criterion were null responders (<2 $\log_{10}$ decline at treatment week 12 and no SVR) to PR. SVR rates among null responders (identified by the more low cut off at week 4) were 30% for Group 2 and 28% for Group 3.[5,10] AASLD guidelines advise caution in using BOC in null responders until further evidence is available.[2]

The FDA also has approved triple therapy for cirrhotic patients, because FDA analysis and post-hoc analysis by RESPOND-2 researchers has attributed the 7% numerical difference in treatment response between Groups 2 and 3 to cirrhotic patients. Therefore, drug-labeling recommends response-guided regimen (i.e., 32 weeks of BOC therapy) for non-cirrhotic, treatment-experienced patients and the fixed-dose regimen (44 weeks of BOC therapy) for the cirrhotic patients.[5,12]

The SPRINT-2 trial and FDA post-hoc analyses established a 24-week triple therapy regimen for treatment-naïve early responders and a 32-week triple therapy regimen with an additional 12 weeks of PR for late responders. The RESPOND-2 trial established a 32-week triple therapy regimen for treatment-experienced early responders and a 32-week triple therapy regimen with an additional 12 weeks of PR for treatment-experienced late responders. Post-hoc analysis established a 44-week triple therapy regimen for all cirrhotic patients and null responders.

Internal and external validity concerns with phase 3 clinical trials included limited or no tracking of adherence, extensive inclusion and exclusion criteria, probability of compromised blinding, unresolved treatment durations for late responders, cirrhotic patients, null responders, and black patients; and whether similar efficacy and safety results can be achieved in a general clinical setting, as triple therapy requires strict and frequent monitoring of serum HCV RNA, adherence by clinicians to stopping rules and treatment regimens, management of an extensive list of probable and actual drug-drug interactions, and close monitoring for adverse reactions. The emergence of drug resistance, especially in patients who have had a prior non-response, are non-adherent to therapy, or are intolerant of optimal PR doses also is a concern.[13]

Despite these unknowns, triple therapy has the benefit of improved SVR rates for adult patients who are treatment-naïve or who are treatment-experienced, particularly prior partial responders and relapsers.

DRUG SAFETY

Safety issues arising from clinical trials focused on anemia and neutropenia. For the phase 2 study (SPRINT-1) and two phase 3 trials combined, anemia was the most common adverse event and occurred at a greater frequency for subjects taking BOC-containing regimens (49%) v. PR alone (29%).[1] The frequency of thrombocytopenia and neutropenia also were greater, but less so. The higher frequency of anemia in those taking BOC-containing regimens led to a greater frequency of RIB dose reductions and erythropoietin use. Erythropoietin use in HCV is off-label. [1,4,5,12] Finally, three, possibly four, serious infections occurring in proximity to severe neutropenia are of concern, as more infections may occur as BOC-containing regimens are used in the general clinical setting. In clinical trials, BOC was not associated with a substantial incidence of dermatologic effects such as rash or pruritus. The discontinuation rates for adverse events for subjects receiving BOC-containing regimens versus PR alone were similar, 13% and 12%, respectively.[1,12]

Serious (REMS, Black Box Warnings, and Contraindications):[1] Contraindications to peginterferon alfa and ribavirin also apply.
Triple therapy is contraindicated in women who are or may become pregnant and men whose female partners are pregnant. Because RIB is associated with significant teratogenic or embryocidal effects, female patients and female partners of childbearing age should obtain a negative pregnancy test before therapy and use two effective contraceptive methods during and for 6 months following treatment. Female patients should use two effective non-hormonal contraceptives. Concomitant use of Boceprevir with medications that have a narrow therapeutic index and are highly dependent on CYP3A4/5 is contraindicated. Concomitant use of Boceprevir with medications that strongly induce CYP3A4/5 and may result in reduced efficacy of Boceprevir is contraindicated. Serious adverse reactions requiring discontinuation of Boceprevir include anemia and neutropenia.

Monitoring:[1] Monthly pregnancy tests; CBC pretreatment and weeks 4, 8, and 12, of BOC therapy and as appropriate; HCV-RNA levels at weeks 4, 8, 12, and 24, at the end of treatment, during follow-up, and as clinically indicated

Tolerability:[1,12] In phase 2 and 3 studies, serious adverse reactions occurred in 11% of subjects receiving triple therapy and 8% receiving PR alone. Dose modifications (generally of PR) due to anemia occurred twice as often in subjects treated with triple therapy (26%) compared to PR alone (13%). The treatment discontinuation rate due to anemia was 1% for both subjects treated with triple therapy and subjects treated with PR. The proportion of subjects who received an ESA was 43% for subjects treated with triple therapy v. 24% for subjects treated with PR. The proportion of subjects receiving a transfusion for the management of anemia was 3% for subjects receiving triple therapy compared to <1% for PR alone. The proportion of subjects with neutrophil counts <0.5 x 10^9/L was 7% for subjects receiving triple therapy v. 4% of subjects receiving PR alone. Three subjects experienced severe or life-threatening infections associated with neutropenia, and two subjects experienced life-threatening neutropenia while receiving triple therapy. Thromboembolic events were reported among subjects receiving triple therapy and among those receiving PR alone. However, no causality assessment can be made as these events are not only known to be associated with ESA use but also PR use and underlying disease.

Pregnancy/Lactation:[1] Although the pregnancy category of BOC alone is B, the pregnancy category for combination therapy is X, since RIB has caused birth defects or fetal deaths in all animal species studied and PEG is abortifacient in animals. Animal studies indicate nursing infants could be exposed to BOC; therefore, the benefits must be weighed against the risks of discontinuing nursing or discontinuing treatment with BOC.

Unanswered safety questions:[1] What will be the incidence of neutropenia-associated severe or life-threatening infections in the general clinical setting? What is the safety of ESA use in patients receiving triple therapy?

Dose Index (efficacy/toxic):[1] *The* effective dose is 800 mg every 7–9 hours. Healthy human subjects have taken daily doses of 3600 mg for 5 days without ill effect.

Several other unanswered questions remain with regard to treatment and safety, including:
What is the comparative efficacy of RGT versus fixed-dose therapy?
How do liver-transplant or HIV or HBV co-infected patients respond to TPR therapy?
What is the dosing for pediatric patients?
Would patients who previously failed treatment with a BOC-containing regimen respond to a repeat course of therapy?
What is the long-term clinical impact of emergence or persistence of BOC-associated resistance amino acid substitutions?
What is the impact of BOC exposure or treatment failure on the efficacy of other HCV NS3/4 protease inhibitors, such as telaprevir?
What anti-HCV activity does BOC have against non-genotype 1 HCVs?

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexicomp, USP Online LASA Finder, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexicomp	USP Online	ISMP	Clinical Judgment
LA/SA for boceprevir (generic) or Victrelis™(brand)	None	None	None	None

ADVERSE REACTIONS[1]

Table 3
Adverse Events Reported in ≥10% of Subjects Receiving the Combination of VICTRELIS with PegIntron/REBETOL and Reported at a Rate of ≥5% than PegIntron/REBETOL alone

Adverse Events	Previously Untreated (SPRINT-1 & SPRINT-2)		Previous Treatment Failures (RESPOND-2)	
	Percentage of Subjects Reporting Adverse Events		Percentage of Subjects Reporting Adverse Events	
Body System Organ Class	VICTRELIS + PegIntron + REBETOL (n=1225)	PegIntron + REBETOL (n=467)	VICTRELIS + PegIntron + REBETOL (n=323)	PegIntron + REBETOL (n=80)
Median Exposure (days)	**197**	**216**	**253**	**104**
Blood and Lymphatic System Disorders				
Anemia	50	30	45	20
Neutropenia	25	19	14	10
Gastrointestinal Disorders				
Nausea	46	42	43	38
Dysgeusia	35	16	44	11
Diarrhea	25	22	24	16
Vomiting	20	13	15	8
Dry Mouth	11	10	15	9
General Disorders and Administration Site Conditions				
Fatigue	58	59	55	50
Chills	34	29	33	30
Asthenia	15	18	21	16
Metabolism and Nutrition Disorders				
Decreased Appetite	25	24	26	16
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	19	19	23	16
Nervous System Disorders				
Dizziness	19	16	16	10
Psychiatric Disorders				
Insomnia	34	34	30	24
Irritability	22	23	21	13
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea Exertional	8	8	11	5
Skin and Subcutaneous Tissue Disorders				
Alopecia	27	27	22	16
Dry Skin	18	18	22	9
Rash	17	19	16	6

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose
200 mg	Capsule	Oral	800 mg three times daily (7-9 hour apart)	None	None for mild, moderate, or severe hepatic impairment. Efficacy and safety not established in decompensated cirrhosis.	Safety and effectiveness not established	Response to therapy in patients ≥ 65 years old is uncertain; therefore, caution should be exercised

OTHER DOSING CONSIDERATIONS:

- Administer with a meal or light snack.
- **Patients without cirrhosis who are treatment-naïve or previous partial responders or relapsers to interferon and ribavirin therapy should i**nitiate therapy with PR for 4 weeks (i.e., from week 1 through week 4), then triple therapy as follows:
  - Treatment-naïve patients with undetectable HCV-RNA at weeks 8 and 24 should complete triple therapy at week 28, and those with detectable HCV-RNA at week 8 and undetectable HCV-RNA at week 24 should complete triple therapy at week 36 and continue with PR only through week 48.
  - Previous partial responders or relapsers with undetectable HCV-RNA at weeks 8 and 24 should complete triple therapy at week 36, and those with detectable HCV-RNA at week 8 and undetectable HCV-RNA at week 24 should complete triple therapy at week 36 and continue PR alone through week 48.
- Patients with compensated cirrhosis should receive 4 weeks PR followed by 44 weeks triple therapy plus PR.
- Response-guided therapy was not studied in patients previously treated with PR who had <2-$\log_{10}$ decrease in HCV-RNA by treatment week 12. If treated, these patients should receive 4 weeks PR followed by 44 weeks triple therapy. Also, consider giving treatment-naïve patients who were poorly responsive to interferon at treatment week 4 with 4 weeks of PR followed by 44 weeks triple therapy.
- Dose reduction of Boceprevir is not recommended.
- Discontinue triple therapy for all patients with HCV-RNA ≥100 IU/mL at week 12 or confirmed, detectable HCV-RNA at week 24.
- See prescribing information for PEG and RIB for other dosing considerations.
- Although currently underway; at this time there are no published studies establishing the efficacy and safety of Boceprevir in patients co-infected with HCV and HIV or hepatitis B or in organ transplant patients.
- Note: Treatment duration recommendations differ for some subgroups from durations in the phase 3 trials.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	Not reported
Protein Binding	75%
Elimination	79% in the feces, 9% in urine
Half-Life	3.4 hours
Metabolism	Aldoketoreductase (primary) and CYP3A4/5

*Food, regardless of meal type, affects exposure to BOC, with 65% increase in exposure relative to fasting state.

PHARMACOGENETICS[1]

Retrospective studies indicate triple therapy increased SVR rates regardless of interleukin-28B genotype in treatment-naïve and treatment-experienced patients. However, these results should be viewed cautiously, because the sample size was small and the substudy populations may not represent the full trial populations.

ALLERGIES/INTERACTIONS[1,12]

Drug-Drug:

BOC is a substrate and strong inhibitor of CYP3A4/5 and a substrate and potential inhibitor of P-glycoprotein. Although BOC is primarily metabolized by aldoketoreductase (AKR), BOC may be co-administered with AKR inhibitors. Co-administration of BOC with drugs that induce or inhibit CYP3A4/5 could decrease or increase BOC exposure.

Drugs contraindicated (adverse reaction): alfuzosin (hypotension), rifampin (loss of virologic response to BOC), ergot derivatives (acute ergot toxicity), St. John's wort (loss of virologic response to BOC), lovastatin or simvastatin (myopathy), pimozide (cardiac arrhythmias), sildenafil or tadalafil dosed for pulmonary arterial hypertension (PDE5 inhibitor-associated adverse events), triazolam or oral midazolam (increased sedation or respiratory depression), cisapride (cardiac arrhythmias), carbamazepine or phenobarbital or phenytoin (loss of virologic response to BOC), and drosperinone (hyperkalemia).

Dozens of other drug interactions with BOC are predicted or have been confirmed via studies. Several of these drugs require dose adjustments or clinical monitoring when used concomitantly with BOC. Drug interaction trials have yet to be conducted, or were flawed, for some key drugs or drug classes: a sensitive P-glycoprotein substrate such as digoxin, methadone, oral contraceptives, and antidepressants.

Food-Drug: No food-drug interactions have been reported.[1]

APPENDIX 1
Suggested PA Criteria

Hepatitis C Oral Protease Inhibitors/Triple Therapy

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code:	**Yes:** Go to #4	**No:** Pass to RPh, Deny For Appropriateness
4. Does the patient have documented HCV genotype 1? Record Genotype:	**Yes:** Go to #5	**No:** Pass to RPh, Deny For Appropriateness
5. Does the patient have a pre-treatment viral load (since diagnosis)?	**Yes:** Go to #6	**No:** Pass to RPh; Deny For Appropriateness; Recommend viral load
6. Is the patient also being prescribed peginterferon alfa-2a or -2b and ribavirin?	**Yes:** Go to #7	**No:** Pass to RPh, Deny For Appropriateness
7. Has prior authorization been granted for peginterferon alfa-2a or -2b and ribavirin or does patient meet prior authorization criteria for pegylated interferon-alfa?	**Yes**: Go to #8	**No**: Pass to RPh; Deny for appropriateness
8. Is the request for continuation of therapy? (Patient has been on triple therapy with a oral antiviral agent in preceding 6 weeks)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #9
9. Has the patient previously been treated with boceprevir or telaprevir?	**Yes**: Pass to RPh, Deny for appropriateness	**No:** Go to #10
10. Is the request for telaprevir 750mg (two tabs) TID for 12 weeks?	**Yes:** Approve for 6 weeks to allow for 4 week viral load check to continue for a maximum of 12 weeks	**No:** Go to #11 (If dose is different pass to RPh for appropriateness)
11. Is the request for boceprevir 800mg (four tabs) TID and the patient has completed 4 weeks of lead-in treatment with ribavirin and peginterferon?	**Yes:** Approve for 10 weeks to allow for 8 week viral load check to continue for a maximum of 24, 32, or 40 weeks based on response	**No:** Pass to RPh; Deny for appropriateness

Continuation of Therapy- Telaprevir		
1. Is the patient treatment-naïve or a prior relapse patient and has undetectable HCV RNA or measured at 4 and 12 weeks?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for 12 weeks (total treatment duration of 24 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
2. Is the patient treatment-naïve or a prior relapse patient and has detectable (1000 IU/mL or less) at Weeks 4 and/or 12	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
3. Is the patient a prior partial or null responder?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness)
4. Is the patient treatment-naïve with documented cirrhosis that has undetectable HCV-RNA at weeks 4 and 12?	**Yes:** Approve as follows: • Approve additional 6 weeks of triple therapy with telaprevir, peginterferon, and ribavirin (total 12 weeks), followed by continued dual therapy with peginterferon and ribavarin for additional 36 weeks (total treatment duration of 48 weeks).	**No:** DENY (Medical Appropriateness) Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of therapy is recommended in all patients with (1) HCV-RNA levels of greater than or equal to 1000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24.
***TREATMENT FUTILITY RULES** Week 4 or Week 12: HCV-RNA greater than 1000 IU/mL: Discontinue INCIVEK and peginterferon alfa and ribavirin (INCIVEK treatment complete at 12 weeks) Week 24: Detectable Discontinue peginterferon and ribavirin. If peginterferon alfa or ribavirin is discontinued for any reason, INCIVEK must also be discontinued		

Continuation of Therapy- Boceprevir		
1.Is the patient treatment-naïve and have undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 14 weeks of boceprevir for total treatment duration of 28 weeks (4 week lead-in, 24 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
2. Is the patient treatment-naïve and have detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
3. Is the patient a previous partial responder or relapser and has undetectable HCV RNA at treatment weeks 8 and 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir for total treatment duration of 36 weeks (4 week lead-in, 32 weeks triple therapy)	**No:** DENY (Medical Appropriateness)
4. Is the patient a previous partial responder or relapser and has detectable HCV RNA at treatment week 8 and undetectable at week 24?	**Yes:** Approve as follows: • Approve additional 22 weeks of boceprevir followed by continued dual therapy with peginterferon and ribavirin for 16 weeks for total treatment duration of 48 weeks (4 week lead-in, 32 weeks triple therapy, 12 weeks dual therapy)	**No:** DENY (Medical Appropriateness)
5. Does the patient have documented cirrhosis or is documented as a null responder and does not meet the futility rules at treatment weeks 8,12, and 24?	**Yes:** Approve as follows: • Continue triple therapy with boceprevir for a total treatment duration of 48 weeks (4 week lead-in, 44 weeks triple therapy).	**No:** DENY (Medical Appropriateness)
***TREATMENT FUTILITY RULES** If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.		

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Class Update: Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), and Direct Renin Inhibitors (DRIs)

EXECUTIVE SUMMARY:

Month/Year of Review: January 2012
New Product for review: azilsartan (Edarbi)
Manufacturer: Takeda Pharmaceuticals
Last Oregon Review: Feb 2010

Dossier received: Yes

Source Document: DERP

Available Alternatives

Current Preferred Agents:

ACEIs
benazepril
captopril
enalapril
fosinopril
lisinopril
moexipril
quinapril
ramipril
trandolapril

Thiazide Combo:
benazepril-Hydrochlorothiazide
Benicar HCT (olmesartan-hydrochlorothiazide)
captopril/hydrochlorothiazide
enalapril-Hydrochlorothiazide
fosinopril-Hydrochlorothiazide
lisinopril-Hydrochlorothiazide
losartan-Hydrochlorothiazide
Micardis HCT (telmisartan-hydrochlorothiazide)
moexipril-Hydrochlorothiazide
quinapril-Hydrochlorothiazide

ARBs
Benicar (olmesartan)
losartan
Micardis (telmisartan)

Current Non-Preferred Agents:

ACEIs
Aceon (perindopril)

ARBs
Atacand (candesartan)
Teveten (eprosartan)
Avapro (irbesartan)
Diovan (valsartan)

DRIs
Tekturna (aliskiren)

Combo Products:
Azor (amlodipine/olmesartan)
Exforge (amlodipine/valsartan)
Twynsta (telmisartan/amlodipine)
Valturna (aliskiren/valsartan)
Amturnide (aliskiren/amlodipine/hctz)
Tekamlo (aliskiren/amlodipine)
Lotrel (amlodipine/benazepril)
Tarka (trandolapril/verapamil)
Tekturna HCT

Previous Conclusions by HRC:

1. There are no clinically significant differences among ACE-Is or ARBs.
2. Combination therapy with an ACE-I and an ARB produces a reduction in proteinuria in nondiabetic proteinuria or chronic kidney disease but produced no clinically significant difference in other measures of renal function.
3. Rates of cough were lower with ARBs than ACE-Is however overall rates of withdrawal were the same.
4. There were no included studies that evaluated comparative effectiveness/ efficacy and harms between aliskirin as monotherapy or for combination therapy with ACE-I and ARB.
5. There was no significant difference found between ARBS and ACEIs for subgroups based on age, ejection fraction, or NYHA functional class

Reason for Review:

Since the last OR review in 2010 a high quality systematic review was performed for the Agency for Healthcare Research and Quality (AHRQ) to update their previous comparative effectiveness review to evaluate the long-term benefits and harms of ACEIs, ARBs, and DRIs for treating essential hypertension in adults[1]. This review looked at available comparative effectiveness research of DRIs while the previous DERP review only had placebo-controlled studies for the DRIs. Since this systematic review, a new ARB was added to the market. Azilsartan was approved by the FDA in February 2011 for treatment of hypertension[2]. There is also new evidence showing no advantage of combination therapy with an ACEI and ARB on clinical outcomes and more adverse effects associated with the combination.[3] In December, the ALTITUDE study with aliskiren was terminated due to the unlikely benefit from treatment and the higher incidence of adverse events identified in this study. In the treatment arm there was an increased incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension. This was the first trial that evaluated the DRI aliskiren for longer than one year in high risk cardiovascular and renal patients.

Issues:

- Is there any new evidence that there is a meaningful difference in ACEIs, ARBS, and DRIs in long term clinical outcomes or safety that would precipitate changes to previous recommendations?
- Is there any evidence that azilsartan is more effective than currently available medications in the PDL drug class?
- Should azilsartan be added as a preferred agent on the OHA PDL class?

Conclusions:

The AHRQ systematic review concluded that the strength of evidence remains high for equivalence between ACEIs and ARBs for blood pressure lowering and use of a single antihypertensive agent, and a meaningful difference between ARBs and ACEIs only for short-term adverse events due to cough. The overall incidence of cough varies widely in clinical trials and has been reported to be in the range of 5 to 35% and a much lower incidence has been described in studies of patients presenting for the evaluation of chronic cough[4]. The evidence looked at since the initial review did not change any conclusions made regarding long term cardiovascular outcomes, quality of life, progression of renal disease, medication adherence, or persistence rates of angioedema, or differences in key patient subgroups and the strength of evidence remains low to moderate. There was insufficient evidence to reach conclusion for the DRIs for any outcomes of interest.

Azilsartan is the eighth ARB indicated for the treatment of hypertension to lower blood pressure either alone or in combination with other agents. Although recent studies have demonstrated that azilsartan is more effective than olmesartan, valsartan, and ramipril at lowering systolic BP[5-8], there is no evidence showing an impact in clinical cardiovascular outcomes, preventing mortality, or showing reduction in cardiovascular risk in patients with hypertension. In addition, other established ARBs have evidence for multiple indications including CHF, diabetic nephropathy, stroke prevention, and treatment of hypertension in pediatric patients while azilsartan is only indicated for blood pressure lowering. In short term studies, azilsartan seems to be well tolerated with the most common side effects being diarrhea and headache. Still, long term safety is unclear as a very limited number of patients have received the drug for at least one year. Losartan is currently the only ARB available in generic form.

Use of azilsartan in Specific Subpopulations:

Pediatric Use: Safety and effectiveness in patients under 18 years of age have not been established.

Geriatrics: No dose adjustment necessary. Abnormally high serum creatinine values were more likely to be reported for patients age 75 or older.

Gender, race, and ethnicity: Azilsartan was effective in reducing blood pressure regardless of the age, gender, or race of patients, but the effect was smaller in black patients, approximately half, who tend to have lower renin levels. This is similar to other drugs in this class.

Place in therapy:
The value of azilsartan remains unclear until longer term studies evaluating clinical outcomes and additional indications are conducted.

Recommendations:
1. Due to lack of comparative effectiveness research for any clinical outcomes, recommend maintaining all DRI's and products containing a DRI as non-preferred on the current PDL.
2. Due to lack of long term studies demonstrating reduction of cardiovascular events and mortality or long-term safety data compared to multiple alternatives, recommended making azilsartan a nonpreferred ARB.
3. No significant evidence exists since last OHA class review that would mandate changes to PDL medications based on comparative effectiveness research. Recommend comparing costs of agents for any further additions or eliminations to preferred products.

I. Background

An estimated 80 million Americans have cardiovascular disease and 73.6 million of these people have hypertension.[9] The renin-angiotensin-aldosterone system (RAAS) has long been considered a significant contributor to CVD through increases in blood volume, arterial pressure, and vascular lesions. Agents used to modulate the RAAS include ACEIs, ARBS, and DRIs.[8] The strength of the evidence in support of renin-angiotensin system blockade has led to incorporation of ACE-Is and ARBs into important clinical guidelines in the treatment of several medical conditions including hypertension, congestive heart failure, and renal disease. The recently updated guidelines published by the National Institute for Health and Clinical Excellence (NICE) recommend treating hypertension with an ACE or a low cost ARB if an ACE is not tolerated as step 1 treatment in patients under 55 years old secondary to evidence showing no meaningful difference between ACEIs and ARBs on major clinical outcomes including death, cardiovascular events, stroke, and diabetes. They also recommend not combining an ACE and an ARB for treatment of hypertension due to evidence showing no advantage on clinical outcomes and more associated adverse effects when using the combination[3]. Although outdated, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) recommends an ACEI or ARB for patients with hypertension who have heart failure, diabetes, or chronic kidney disease.[10] The Kidney Disease Outcome Quality Initiative guidelines recommend ACEIs or ARBs for patients with diabetic or non-diabetic proteinuric renal disease[11]. ACEIs are also recommended in all patients with symptoms of heart failure and reduced ejection fraction and ARB's are recommended as alternatives[12].

Hypertension is a highly prevalent disease that is a major risk factor for cardiovascular disease. There is growing evidence for increased CV complications and mortality associated with hypertension and higher BP levels, including an increased rate of death due to stroke and ischemic heart disease. The Framingham Heart Study found an association between BP category and incidence of CV disease and data from the National, Heart, Lung, and Blood Institute indicate that hypertension is associated with a shorter overall life expectancy. Therapies aimed at the RAAS are frequently used for the lowering of blood pressure as well as in other indications such as heart failure, myocardial infarction, diabetes, and renal disease.

Current guidelines recommend a step-wise approach from lifestyle modifications to monotherapy or combination therapy, as many patients cannot reach goal on one drug and will require two or more antihypertensive agents selected from different classes. The target BP for patients with hypertension is < 140/90 mm Hg and <130/80 for whose with diabetes mellitus, heart disease, or renal disease. Despite the availability of a wide selection of antihypertensive agents, optimal BP control remains a challenge. Although ACEIs, ARBS, and DRIs all target the renin system, they all do so in a slightly different way, targeting the pathway at different points and questions still arise whether there are any differences in these classes are in fact equivalent and how they compare in effecting clinical outcomes

II. Systematic Reviews:

AHRQ Review[1] :

Published in June 2011
Compared the ACEIs, ARBs, and DRIs in both efficacy and safety in adult patients with hypertension. Clinical outcomes of interest were blood pressure control, mortality, morbidity, safety, persistence/adherence, cardiovascular risk reduction, and quality of life. They also assessed if there was any evidence showing that different subgroups of patients tolerated the different agents better.

The review included only relevant head to head comparator studies that had a minimum of 12 weeks follow-up.

Did not include studies comparing the newest ARB, azilsartan.

Conclusions:

1. There is high quality evidence that ACEIs and ARBs appear to have similar long-term effects on blood pressure. There is low quality evidence regarding the effects of DRIs on blood pressure and is only based on three studies.
2. There is low quality evidence that shows no difference exists between ACEIs and ARBs regarding mortality and major cardiovascular events due to extremely low numbers of the outcomes that were reported. There is insufficient evidence comparing DRIs to detect a difference in these outcomes.
3. There is low quality evidence that there are differences between ACEIs and ARBs in quality of life and insufficient evidence comparing DRIs.
4. There is high quality evidence that there is a difference in withdrawals due to adverse events between ACEIs and ARBs and this can be contributed to an increased risk of cough associated with the ACEIs than ARBs. Cough is the only adverse event shown to have evidence of difference across treatment rates.
5. There is low quality evidence showing no significant difference comparing DRIs and ACEIs in withdrawals due to adverse events.
6. Evidence does not support any conclusions regarding comparative effectiveness or safety in patient subgroups based on age, race, ethnicity, sex, comorbidities, and concurrent use of other medications.

Remaining Issues:
There is still little comparative evidence for long-term benefits or harms of ACEIs and ARBs, and DRIs in particular about death or major cardiovascular events. There is very limited comparative effectiveness research for the DRIs versus ACEIs or ARBS with only 3 studies meeting the authors' inclusion criteria for evaluation and reporting.

Further comparative studies are needed to emphasize:

- Subgroups of importance
- Outcomes over several years to compare cardiovascular and cerebrovascular events
- Cancer-related outcomes
- Broader representation of groups to include the elderly and ethnic minorities
- Long-term comparisons of DRIs with ACEIs and ARBs
- Evaluation of differential effects of specific medications that are different than other agents within the class

Although this recent AHRQ systematic review only evaluated outcomes in patients with hypertension the most recent DERP report found similar results when comparing ACEIs and ARBs in clinical outcomes including cardiovascular events, mortality, quality of life, renal function, and symptoms in patients with heart disease, diabetic proteinuria, nondiabetic proteinuria and chronic kidney disease. This report also concluded that ARBs are not different from, nor inferior to, ACEIs.[12]

III. New ARB: Azilsartan

Clinical Findings –

Azilsartan is an ARB indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents. Azilsartan was approved based on the results of seven double-blind, randomized studies involving a total of 5,941 patients with hypertension ranging from 6 weeks to 6 months in duration; two of which have been published and peer reviewed. These studies only evaluated azilsartan's effects on the intermediate biomarker of blood pressure. There is no evidence with long term clinical outcomes assessed. Azilsartan has been compared head to head with the other ARBS olmesartan and valsartan as well as with the ACEI ramipril.[2] The details of the 2 published full-text head to head trials are shown in the evidence table found in Appendix 1.

One double-blind, placebo-controlled, randomized trial compared azilsartan 40mg and 80mg to valsartan 320mg, or olmesartan 40mg daily for 6 weeks. The primary efficacy end point was the change from baseline in 24-hour mean SBP. Azilsartan 80mg showed a statistically significant greater change in baseline in mean difference compared to both valsartan and olmesartan (-4.3 and -2.5 respectively) while azilsartan 40mg had a statistically significant mean difference in BP compared to valsartan only -3.2) and was noninferior to olmesartan. Safety and tolerability were similar among the placebo and all active treatments[6].

In another double-blind, randomized, placebo-controlled trial, patients were randomized to placebo, azilsartan 20mg, 40mg, or 80mg or olmesartan 40mg daily for 6 weeks. The change in 24-hour SBP was significantly greater with azilsartan 80mg compared to olmesartan 40mg (mean difference -2.1), while azilsartan 40mg was found to be noninferior[8].

Both of these studies uses similar inclusion and exclusion criteria and were rated as fair quality. They both had extensive exclusion criteria and had unclear information regarding their randomization methods. In subgroup analysis, both studies saw differences only in the black population which is consistent with previous findings.

There are additional comparative effectiveness studies conducted evaluating blood pressure that have not been published. The abstracts for these were presented at the 2010 European Meeting on Hypertension and can be found in the Journal of Hypertension. Preliminary results from a randomized, double blind study showed that azilsartan 40mg and 80mg reduced both clinic and mean 24-hour systolic BP significantly more than did ramipril 10mg and there were less discontinuations due to adverse events and cough with both doses of azilsartan. [14] In another trial, azilsartan was combined with the diuretic chlorthalidone and provided further SBP reduction from baseline and appeared to be superior to the combination of olmesartan and hydrochlorothiazide[15]. Additive effects on blood pressure of amlodipine combined with azilsartan have also been demonstrated.[16]

The short duration of these studies remains an important limitation making it difficult to evaluate the long-term benefit and side effects of azilsartan. There is no evidence on the possible role of azilsartan in preventing mortality and CV morbidity.

Clinical pharmacology [17]

Azilsartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues. Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Drug safety [17]

Black Box Warning: Avoid use in pregnancy. If pregnancy is detected, azilsartan should be discontinued as soon as possible to avoid serious injury or even death to the developing fetus.

Pregnancy/Lactation rating: Pregnancy Category C (first trimester) and D (second and third trimesters).

Dose Index (efficacy/toxic): Limited data are available related to overdosage in humans. During controlled clinical trials in healthy subjects, once daily doses up to 320 mg of azilsartan were administered for 7 days and were well tolerated.

Common Drug-Related Adverse Events[17]**:**

Treatment with azilsartan was well-tolerated with an overall incidence of adverse reactions similar to placebo. The most common adverse effect was diarrhea with an incident of 2%.The rate of withdrawals due to adverse events in placebo-controlled monotherapy and combination therapy trials was 2.4 % for placebo, 2.2% for azilsartan 40 mg, and 2.7% for azilsartan 80 mg. The most common adverse event leading to discontinuation, hypotension/orthostatic hypotension, was reported by 0.4% (8/2146) patients randomized to azilsartan 40 mg or 80 mg compared to 0% (0/801) patients randomized to placebo. Generally, adverse reactions were mild, not dose related and similar regardless of age, gender and race.

Other adverse reactions that have been reported with an incidence of >0.3% and greater than placebo are:
Gastrointestinal Disorders: nausea
General Disorders and Administration Site Conditions: asthenia, fatigue
Musculoskeletal and Connective Tissue Disorders: muscle spasm
Nervous System Disorders: dizziness, dizziness postural
Respiratory, Thoracic and Mediastinal Disorders: cough

Appendix 1:
COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Cardiovascular Mortality
3) Cardiovascular Hospitalizations
5) Withdrawals due to adverse events

Primary Study Endpoint: 1) Change from baseline in 24-hour mean SBP by ambulatory blood pressure monitoring.

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population/ Duration	N	Efficacy Results[2]	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH[3]	Quality Rating[4]; Comments
1.White et al RCT, DB[6] 491-019	1. azilsartan (AZ) 40mg 2. Azilsartan (AZ) 80mg 3. Valsartan (VAL 320mg 4. Olmesartan (OLM) 40mg 5. placebo	Adults whose SBI was between 150 and 180 and whose mean 24-hour SBP was between 130 and 180 Mean age 56 54% men Duration = 6 weeks	1. 280 2. 285 3. 254 4. 290 5. 154	<u>Change in 24 h mean baseline SBP (mean treatment difference in mm Hg)</u> <u>*Vs. Placebo*</u> AZ 40mg -13.2 P<0.001 AZ 80mg -14.3 P<0.001 VAL 320mg -9.9 P<0.001 OLM 40mg -11.7 P<0.001 <u>*Vs. Olmesartan*</u> AZ 40mg -1.4 95% CI (-3.3,-0.5) P=0.136 AZ 80mg -2.5 95% CI (-4.4,-0.6) P= 0.009 <u>*Vs. Valsartan*</u> AZ 40mg -3.2 P=0.001 AZ 80mg -4.3 95% CI (-6.3,-2.4) P<0.001	 N/A N/A N/A N/A NS N/A N/A N/A	<u>Discontinued due to adverse events:</u> 1. 7 (2.5%) 2. 9 (3.2%) 3. 8 (2.8%) 4. 6 (2.1%) 5. 4 (2.6%)	NS	Fair: Significant cardiovascular exclusion criteria making it hard to generalize to population Eligible patients underwent a 3 to 4 weeks washout period before randomization Among all randomized patients, 96 % were included in the data analysis Unclear if allocation concealment or appropriate randomization took place There was a marginally statistically significant treatment difference between black and white patients *Clinical outcomes of Mortality, Cardiovascular Mortality, and Cardiovascular Hospitalizations not reported

2.Bakris, et al[8] RCT, DB 491-008	1. azilsartan (AZ)20mg 2. Azilsartan (AZ) 40mg 3. Azilsartan(AZ) 80mg 4. Olmesartan (OLM) 40mg 5. placebo	Adults whose SBI was between 150 and 180 and Whose 24 hr mean SBP was between 130 and 170 Mean age 58 Duration = 6 weeks	1. 283 2. 283 3. 285 4. 282 5. 142	<u>Change in 24 h mean baseline SBP (mean treatment difference in mm Hg)</u> <u>*Vs. Placebo*</u> AZ 20mg -10.8 95%CI (-13.2,-8.3) P<0.001 AZ 40mg -12.1 95%CI (-14.5,-9.7) P<0.001 AZ 80mg -13.2 95%CI (-15.6,-10.8) P<0.001 OLM -11.2 95%CI (-13.6,-8.8) P<0.001 <u>*Vs. Olmesartan*</u> AZ 20mg -0.4 95%CI (-1.6,-2.4) P=0.687 AZ 40mg -0.92 95%CI (-2.9,1.0) P=0.352 AZ 80mg -2.1 95%CI (-4.0.-0.1) P=0.038	 N/A N/A N/A N/A NS NS N/A	Discontinued due to adverse events: 1. 11(3.9%) 2. 3(1.1%) 3. 6(2.1%) 4. 4(1.4%) 5. 6(4.2%)	 NS	Fair; Significant cardiovascular exclusion criteria making it hard to generalize to population Unclear if allocation concealment or appropriate randomization took place Black population subgroup demonstrated a trend for less BP reduction in all active treatment groups compared with Caucasians, but a trend of greater efficacy with azilsartan 80mg compared with olmesartan 40mg Low rates of attrition. *Clinical outcomes of Mortality, Cardiovascular Mortality, and Cardiovascular Hospitalizations not reported

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, STEMI – ST-segment elevation myocardial infarction, NSTEMI – non-ST-segment elevation myocardial infarction

Appendix 2 : Specific Drug Information

DOSE & AVAILABILITY:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
40mg	Tab	PO	Daily	None	None	Not Established	None	Caution in patients with Volume or Salt-depleted Patients. Consider starting with lower 40mg dose for those on high dose diuretics.
80mg	Tab	PO	Daily	None	None	Not Established	None	

Pharmacokinetics

Parameter	Result
Oral Bioavailability	60%
Cmax	1.5-3 hours
Protein Binding	>99%
Elimination	Feces 55% Urine 42% Metabolite 15%
Half-Life	11 hours
Metabolism	O-dealkylation decarboylation

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Month/Year of Review: January 2012
PDL Class: Antivirals: HSV

Date of Last Review: September 2010
Source Document: PS Report

Current Preferred Agents:
Acyclovir, oral (capsule, tablet, oral suspension)

Current Non-Preferred Agents:
Famciclovir, oral
Valacyclovir, oral
Acyclovir (Zovirax®), topical
Penciclovir (Denavir®), topical
Docosanol (Abreva®), topical

Previous Conclusions and Recommendations:

1. The oral agents which are approved for herpes infections include acyclovir (Zovirax), famciclovir (Famvir), and valacyclovir (Valtrex). Based on available data, all of the agents have similar efficacy and adverse effects.
2. The 2006 CDC STD recommendations for genital herpes indicate no preference for any one of these three agents over another. Patients presenting with an initial or a recurrent episode of genital HSV infection should be treated with any one of the three agents. Chronic suppressive therapy for patients with frequent recurrences may include any one of the three agents.
3. All three agents have similar efficacy for the treatment of herpes zoster, and recent guidelines support the use of any of the three agents for first line therapy.
4. Both acyclovir and valacyclovir are approved for the treatment of varicella (chickenpox).
5. These drugs are primarily used for below the line conditions.
6. Recommend including one or more agents from this category on the PDL

PA Criteria/QL: Patient must have an ICD9 diagnosis for uncomplicated herpes simplex **AND** documentation of a disease state or medication that causes immunosuppression. Oral acyclovir does not require PA. (Appendix B)

Methods:

Search Strategy
A MEDLINE OVID search was conducted using the following search terms:
Herpes Genitalis, Herpes Simplex, Herpesvirus 2, Herpesvirus 1, Herpes Labialis, Herpe$; antiviral, antiviral$, antiviral agents; RCT, randomized control trial, clinical trial, controlled trial
The search was limited to studies conducted with humans in English language publications from 2008 to 2011.

Results:
The MEDLINE search retrieved 65 full citations. After a full review of citations and abstracts, one new head-to-head RCT was identified, but no new placebo-controlled RCTs were identified. Most of the citations identified centered on HSV antiviral effects in patient populations co-infected with HIV; of those, most were observational with an objective to see if HSV antivirals might decrease HIV transmission. The search of the Cochrane website identified a protocol proposed this month (10/2011) to review topical and oral interventions for HSV. The search of the AHRQ, DERP, and VA/DoD websites did not identify any relevant systematic reviews. The search on the FDA websites identified one new approved drug, but no new indications, or safety alerts for preexisting products. The citations and abstracts for all relevant studies are listed in Appendix A.

New FDA-approved drugs:
Acyclovir/hydrocortisone (Xerese®), topical
Xerese was approved by the FDA in 2009 for recurrent herpes simplex labialis. This is a new combination product of 5% acyclovir and 1% hydrocortisone as the active ingredients. It was approved on the basis of one efficacy and two safety trials. The citation and abstract of the efficacy study is listed in Appendix A. This was a randomized, double-blind, placebo controlled trial comparing the combination of acyclovir and hydrocortisone versus acyclovir cream.
Although the study shows Xerese to be statistically significant to acyclovir and placebo in preventing lesions from occurring, the clinical relevance is low.

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Systematic Reviews:
None identified.

Appendix A:

Hull, C.M., Harmenberg, J., Arlander, E., Aoki, F., Bring J, et al. Early Treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: A randomized, double-blind, placebo=controlled, patient initiated clinical trial (2011) J Am Acad Dermatol2011; 64 :696.e1-696.e11.

Background: Prior pilot studies support the use of antiviral medications with topical corticosteroids for herpes simplex labialis (HSL). ME-609 (Xerese, Xerclear) is a combination of 5% acyclovir and 1% hydrocortisone developed for the topical treatment of HSL.
Objectives: The primary study end point was the prevention of ulcerative HSL lesions.
Methods: In all, 2437 patients with a history of HSL were randomized to self-initiate treatment with ME-609, 5% acyclovir in ME-609 vehicle, or ME-609 vehicle (placebo) at the earliest sign of a cold sore recurrence. Cream was applied 5 times/d for 5 days. A total of 1443 patients experienced a recurrence and initiated treatment with ME-609 (n = 601), acyclovir (n = 610), or placebo (n = 232).
Results: Of patients receiving ME-609, 42% did not develop an ulcerative lesion compared with 35% of patients receiving acyclovir in ME-609 vehicle (P = .014) and 26% of patients receiving placebo (P\.0001). In patients with ulcerative lesions, healing times were reduced in the ME-609 and acyclovir groups compared with placebo (P\.01 for both). The cumulative lesion area for all lesions was reduced 50%in patients receiving ME-609 compared with the placebo group (P\.0001). There were no differences among groups in the number of patients with positive herpes simplex virus cultures. The side-effect profile was similar among treatments.
Limitations: The study did not contain a group treated with a topical corticosteroid alone.
Conclusions: ME-609 prevented progression of cold sores to ulcerative lesions and significantly reduced the cumulative lesion area compared with acyclovir and placebo. ME-609 treatment offers additional therapeutic benefit compared with therapy with topical acyclovir alone. (J Am Acad Dermatol 2011;64:696.e1-11.)

Appendix B:

Antivirals, Oral and Topical – HSV

Goal(s): Cover oral and/or topical anti-virals only for covered diagnoses. HSV infections are covered only when complicated by an immunocompromised host.

Antivirals **Length of Authorization: Criteria Specific – up to 1 year**

Preferred Alternatives: **Oral** acyclovir DOES NOT require PA. See PDL list at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.

Requires PA: HIC3 = Q5V

GENERIC	BRAND	ROUTE
Famciclovir	Famvir	Oral
Valacyclovir	Valtrex	Oral
Acyclovir	Zovirax	Topical
Penciclovir	Denavir	Topical
Docosanol	Abreva	Topical

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD9 code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml.	**No**: Go to #3
3. Is the diagnosis uncomplicated herpes simplex ICD9: 054.2, 054.6, 054.73, 054.9?	**Yes:** Go to #4	**No:** Pass to RPh; Go to #7
4. Is the patient immune compromised? Document ICD9 code. • Current (not history of) diagnosis of cancer AND is currently undergoing Chemotherapy or Radiation? Document therapy and length of treatment • Diagnosis of HIV/AIDS?	**Yes:** Approve for the shorter of expected therapy duration or90 days (applies to both topical and oral antivirals) (Immunocompromised Client)	**No:** Go to #5

5. Is client currently taking an immunosuppressive drug? Document drug: (If drug not in list below, Pass to RPh for evaluation) Immunosuppressive drugs include, but are not limited to: **Azathioprine** **Imuran** **Basiliximab** **Simulect** **Cyclosporine** **Sandimmune, Neoral** **Sirolimus** **Rapamune** **Tacrolimus** **Prograf** **Methotrexate** **Rheumatrex** **Hydroxychloroquine** **Plaquenil** **Etanercept** **Enbrel** **Leflunomide** **Arava**	**Yes:** Approve for the shorter of expected therapy duration or: 90 days (applies to topical or oral antivirals ; Immunocompromised Client).	**No:** If Diabetes or Sickle-Cell disease-go to #6. All others go to #7.
6. Does client have Diabetes or Sickle-Cell disease? ***Note**: Diabetes and Sickle-Cell is not considered as immunocompromisng for antivirals as it is for antifungal*	**Yes:** Pass to RPH; Deny, (Not Covered by the OHP).	**No:** Pass to RPH to evaluate for immunosuppression. ➢ If not immunocompromised, Deny (Not Covered by the OHP). ➢ If immunocompromised, approve for 1 year.
7. RPH only All other indications need to be evaluated as to whether they are above the line or below the line diagnosis. • **<u>If above,</u>** viral diagnoses can be approved for treatment course with "prn" renewals. If length of therapy is unknown, please approve for 3 months intervals only (This is an exception to above guidelines and should be discussed with Lead Pharmacist) • **<u>If below,</u>** Deny, (Not Covered by the OHP). • **<u>Deny Non-viral diagnoses</u>** (Medical Appropriateness). • **<u>Deny Viral ICD-9 codes</u>** that do not appear on the OHP list pending a more specific diagnosis code. (Not Covered by the OHP)	**If above the line and clinic provides supporting literature:** approve for length of treatment.	**If below the line:** Deny, (Not Covered by the OHP).

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Drug Class Scan

Month/Year of Review: January 2012
PDL Class: Antivirals: Influenza

Date of Last Review: September 2010
Source Document: PS Report

Current Preferred Agents:
Amantadine
Rimantidine*
Oseltamivir* (Tamiflu®)

*with quantity limit

Current Non-Preferred Agents:
Zanamivir (Relenza®)

Previous Conclusions and Recommendations:

1. Vaccination is the primary method of preventing influenza infection.
2. The CDC currently does not recommend the use of amantadine or rimantadine for the treatment or prophylaxis of influenza A due to viral resistance.
3. The CDC recommends treatment of 2009 influenza A (H1N1) in 'at risk' adults and children with either oseltamivir or zanamivir.
4. Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders.
5. Recommend taking into account current public health recommendations for appropriate populations, duration and dosing schedules.

PA Criteria/QL:
For treatment: Patient must have an OHP covered ICD9 diagnosis AND the antiviral is for the treatment of influenza
For prophylaxis: Patient must have an OHP covered ICD9 diagnosis AND be considered at high risk for complications for influenza
Quantity Limit: Oseltamivir requires PA for therapy exceeding five days

Methods:

Search Strategy
An Ovid MEDLINE search was conducted using the following search terms:
Influenza, human influenza, influenza A virus, influenza B virus, H1N1 subtype influenza A virus, flu, H5N1 subtype influenza A virus; antiviral, antiviral$, antiviral agents; RCT, randomized control trial, randomized control trials, trial$, clinical trial, controlled trial
The search was limited to studies conducted with humans in English language publications from 2008 to present.

Results:
The MEDLINE search retrieved 139 full citations. After a full review of citations and abstracts, no new head-to- or placebo-controlled RCTs using FDA approved agents were identified. Most of the RCTs identified compared oseltamivir with either neuraminidase inhibitors not approved for use in the US, or herbal/naturopathic agents. Many RCTs were related to vaccination. This search produced numerous articles analyzing the 2009 h1N1 pandemic; prevention and treatment were examined in various formats: articles, case studies, reviews, observational studies.

The search of the Cochrane website identified two new proposed protocols in regards to influenza: one to review treatment interventions (proposed 11/2010) and the other to review prevention interventions (5/2010). The current Cochrane review for treatment with neuraminidase inhibitors (last updated 2010) was not included due to lack of quality RCTs. Prior recommendation of oseltamivir over zanamivir has been removed pending more data; a new protocol for review was proposed 6/2011.
The search of the AHRQ, DERP, and VA/DoD websites did not identify any relevant systematic reviews. The search on the FDA websites identified no new approved drugs, no new indications, and one new safety alert.

New FDA-approved drugs:
None identified.

New FDA Indications:
None identified.

New FDA safety alerts:

Medication	Alert Date	FDA Alert
Oseltamivir (Tamiflu®) suspension	July 2011	**Warnings and Precautions:** **ISSUE:** Labeling changes are being made to Tamiflu oral suspension to reduce the possibility of prescribing and dosing confusion that can lead to medication errors. The changes to the product label include: • A change in the concentration of Tamiflu from 12 mg/mL to 6 mg/mL. The lower concentration of Tamiflu is less likely to become frothy when shaken, which helps to ensure an accurate measurement. A change in the measurements of the oral dosing

device from milligrams (mg = weight) to milliliters (mL = volume).
- A change in the dosing table for Tamiflu to include a column for the volume (mL) based on the new 6 mg/mL concentration. Revised container labels and carton packaging. Revised compounding instructions for pharmacies to prepare a 6 mg/mL oral suspension from Tamiflu capsules in an emergency situation only if the commercially manufactured Tamiflu for oral suspension is unavailable.

BACKGROUND: Tamiflu is in a class of medications called neuraminidase inhibitors. These drugs work by stopping the spread of the influenza (flu) virus in the body. Genentech, the manufacturer of Tamiflu for oral suspension, plans to begin distribution of the new 6 mg/mL product in July 2011. The company has instituted a voluntary Take Back Program for wholesale buyers, distributors and pharmacies to remove the 12 mg/mL product from the marketplace. The 12 mg/mL product will remain in the marketplace and in state or national stockpiles until current supplies expire.

RECOMMENDATION: It is important for healthcare professionals to be aware that a patient may potentially receive either concentration (6 mg/mL or 12 mg/mL) from their pharmacy during the next influenza season (2011-2012). Steps should be taken to avoid the potential for a medication error due to confusion between the two concentrations. Prescribers should include the new concentration (6 mg/mL) and dose in milliliters on all prescriptions for Tamiflu for oral suspension.

New Systematic Reviews:
None identified.

Guidelines[1]:

Centers for Disease Control and Prevention: Antiviral agents for the treatment and chemoprophylaxis of influenza[1].

- Antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization.
- Antiviral treatment is recommended as soon as possible for outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions; clinical judgment should be an important component of outpatient treatment decisions.
- Recommended antiviral medications include oseltamivir and zanamivir, on the basis of recent viral surveillance and resistance data indicating that >99% of currently circulating influenza virus strains are sensitive to these medications. Amantadine and rimantadine should not be used because of the high levels of resistance to these drugs among circulating influenza A viruses, but information about these drugs is provided for use if current recommendations change because of the reemergence of adamantane-susceptible strains.

- Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated.
- Antiviral treatment also may be considered on the basis of clinical judgment for any outpatient with confirmed or suspected influenza who does not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset.

Duration of Treatment or Chemoprophylaxis[1]

Treatment: Recommended duration for antiviral treatment is 5 days. Longer treatment courses for patients who remain severely ill after 5 days of treatment can be considered.

Recommended duration is 7 days after exposure.

Chemoprophylaxis: For control of outbreaks in long-term care facilities (e.g. elderly nursing homes) and hospitals**,** CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks, and continuing up to 1 week after the last known case was identified. Antiviral chemoprophylaxis should be considered, especially for elderly long-term care facilities, for all exposed residents, including those who have received influenza vaccination.

References:

1. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM, Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Surveill Summ 2011 Jan 21;60(1):1-24

Appendix A: PA Criteria

Antivirals - Influenza

Goal(s): To ensure appropriate extended influenza drug use by authorizing utilization in specified patient population.

Length of Authorization: Date of service

Preferred Alternatives: See PDL options at : http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA:

Name of Drug	Brand	Quantity Limits
Zanamivir	Relenza	NA
Oseltamivir	Tamiflu	>5 days therapy requires a PA
Amantadine		NA

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD9 code	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No**: Pass to RPh, DENY (Not covered by the OHP)
3. Is the anitiviral being used to **treat** influenza?	**Yes:** Go to #4.	**No:** Go to #5
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml. Current recommended treatment duration*: - 5 days for the following: Relenza, Tamiflu, - Amantadine: Continue for at least 10 days.	**No**: Approve for 5 days
5. Does the patient have any of the following putting them at increased risk for complications requiring prophylaxis?	**Yes:** Approve for duration of prophylaxis.	**No:** Pass to RPh; Deny, (Not Medically Appropriate)

- High-risk persons during 2 weeks after vaccination before adequate immunity develops - Patients >1 years of age at high risk for complications for whom the vaccine is contraindicated, unavailable or expected to have low effectiveness - Residents in institutions such as nursing homes or long-term care facilities that are experiencing an influenza outbreak - Persons at high-risk of complications of influenza, such as transplant and immunocompromised patients	Current recommended duration of prophylaxis*; Relenza: 10 days for prophylaxis in a household setting, up to 28 days in a community outbreak setting. Tamiflu: at least 10 days following close contact with an infected individual; up to 6 weeks in a community outbreak setting. Amantadine: Up to 4 weeks.	

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Month/Year of Review: January 2012
PDL Class: Oral Beta Blockers

Date of Last Review: July 2009
Source Document: DERP Report

Current Preferred Agents:
Acebutolol HCL
Atenolol
Carvedilol
Labetalol HCL
Metoprolol Tartrate
Nadolol
Propranolol HCL

Current Non-Preferred Agents:
Betaxolol
Bisoprolol
Metoprolol Succinate
Nebivolol, (Bystolic®)
Penbutolol, (Levabutol®)
Pindolol
Timolol

Previous Recommendations:

1. In patients with mild-moderate HF, bisoprolol, carvedilol or metoprolol succinate (ER) reduce mortality.
2. In patients with severe HF, carvedilol or metoprolol succinate (ER) reduce mortality.
3. In patients with recent MI, acebutolol, carvedilol, metoprolol tartrate (IR), propranolol, or timolol reduce mortality. It is important that at least one of these drugs be included in the PDL.
4. All of the β-Blockers reviewed are effective in the treatment of hypertension, but there is no evidence of differences between β-blockers for blood pressure control, survival, or quality of life.
5. All of the β-Blockers reviewed except carteolol reduced anginal attacks in patients in short-term studies that did not allow mortality evaluation.
6. Because of their effectiveness in rate control for atrial fibrillation at least one of either atenolol, bisoprolol, carvedilol, metoprolol succinate (ER), nadolol, pindolol, or propranolol should be included in the PDL.
7. The current evidence does not distinguish a difference among these beneficial β −Blockers that were tested for preventing recurrence and diminishing the severity of migraine headaches: atenolol, bisoprolol, metoprolol tartrate (IR), metoprolol succinate (ER), propranolol, propranolol LA nadolol, or timolol.
8. The current evidence does not distinguish a difference among beneficial β −Blockers that were tested for reducing esophageal variceal re-bleeding: atenolol, nadolol, propranolol, or propranolol LA.
9. There is no evidence of significant differences among β-blockers in safety or adverse effects.
10. There is no evidence of significant differences found for one β-blocker being more effective or associated with fewer adverse effects in subgroups of patients based on demographics (race, ethnicity, gender), use of other medications, or co-morbidities.

PA Criteria/QL: Patient must have a covered ICD9 diagnosis.

Methods:

Search Strategy
A MEDLINE OVID search was conducted using the following search terms:
Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nadolol, Nebivolol, Penbutolol, Pindolol, Propranolol, Timolol, heart failure, myocardial infarction, MI, atrial fibrillation, atrial arrhythmias, atrial flutter, esophageal and gastric varices, angina pectoris, chronic stable angina, migraines, migraine disorders, hypertension, portal hypertension, left ventricular dysfunction

The following limitations were used for the search:
All clinical trials, or clinical trial, or comparative study, or controlled clinical trial, or evaluation studies, or meta analysis, or multicenter study, or randomized controlled trial
English language
Humans
2009-present

Results:
The MEDLINE search retrieved 328 full citations. After a review of citations and abstracts, 48 studies were identified for assessment. Of those, four trials are included below, one placebo and three head-to head trials. A sub-analysis of the SENOIRS trial is a placebo controlled trial that looks at prevention of CV events in CAD patients over 70 on nebivolol. Three head-to-head trails with various beta blockers looked at the following outcomes: reversal of left ventricular dysfunction, prevention of AF in HF patients after post-op CABG, and improvement in symptoms in HF patients with non-selective beta-blockers. Although all of these studies had an outcome for the intervention group over the comparator group, none of these studies should impact current clinical practice. Citations and abstracts for the four included trails are listed in Appendix A.

The search of the Cochrane, AHRQ, DERP, and VA/DoD websites did not identify any relevant new systematic reviews. Search of the FDA website found no new FDA-approved drugs, indications, or relevant safety alerts.

New FDA-approved drugs:
None identified.

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Systematic Reviews:
None identified.

Appendix A:

1 Ambrosio G, Flather M.D, Böhm M, Cohen-Solal A, Murrone A, et al. β-blockade with nebivolol for prevention of acute ischaemic events in elderly patients with heart failure. Heart 2011;97 (3): 209-214.

Objectives: This subanalysis of the Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with Heart Failure (SENIORS) investigates whether treatment with nebivolol, a β-blocker with nitric oxide-releasing properties, can provide additional benefits besides its effects on heart failure (HF), by reducing cardiac ischaemic events in patients with HF of ischaemic aetiology.
Design: A double-blind, randomised, placebo-controlled, multicentre trial of nebivolol in 2128 elderly patients. Patients and interventions: For this analysis, data were extracted for 2128 elderly (≥70 years) HF patients in whom coronary artery disease (CAD) was the underlying aetiology (68.2%; 717 placebo-treated patients and 735 assigned to nebivolol).
Main outcome measures: The main endpoint was the composite of cardiac ischaemic events at 2 year follow-up: death/hospitalisation for myocardial infarction, unstable angina or sudden death, as originally identified in the case report form.
Results: At follow-up, nebivolol treatment was associated with a one-third reduction in the risk of ischaemic events, the composite endpoint occurring in 15.9% of placebo and 10.7% of nebivolol-treated patients (HR 0.68; 95% CI 0.51 to 0.90; p=0.008). This effect was independent of age, gender and ejection fraction. No difference in this composite endpoint was observed in the subgroup of patients of non-ischaemic aetiology.
Conclusions: Nebivolol was effective in reducing cardiac ischaemic events in patients with HF of ischaemic aetiology. The prevention of ischaemic events can be an additional beneficial effect of β-blockade in HF patients with underlying CAD

2 Vinereanu D, Gherghinescu C, Ciobanu AO, Magda S, Niculescu N, et al. Reversal of subclinical left ventricular dysfunction by antihypertensive treatment: A prospective trial of nebivolol against metoprolol. J Hypertens 2011;29(4):809-17.

Objectives: To assess the effects of antihypertensive treatment on subclinical left ventricular dysfunction and to compare the effects of nebivolol with metoprolol.
Methods: This is a prospective, randomized, parallel, active-controlled, PROBE design study (ClinicalTrials.org: NCT00942487) in 60 patients (53 ± 9 years, 67% men) with arterial hypertension, left ventricular hypertrophy, normal ejection fraction, and no coronary heart disease, randomized to either a nebivolol-based or a metoprolol-based treatment, who had conventional and tissue Doppler echocardiography, at rest and during dobutamine stress, at baseline and after 6 months.
Results: SBP and DBP, and resting heart rate decreased by 13, 13, and 12%, respectively, on nebivolol, and by 11, 13, and 7%, respectively, on metoprolol (all, $P < 0.01$). Mean longitudinal early diastolic velocity increased by 16% ($P < 0.05$) on nebivolol compared with 9% (P = not significant) on metoprolol (P = not significant for intergroup differences), whereas flow propagation velocity increased by 34% on nebivolol ($P < 0.05$) and did not change on metoprolol ($P < 0.01$ for intergroup differences). Mean longitudinal displacement increased by 10% on nebivolol ($P < 0.05$) and did not change on metoprolol ($P < 0.05$ for intergroup differences), whereas ejection time increased by 5% on nebivolol ($P < 0.05$) and did not change on metoprolol. All the other parameters of left ventricular function were not different between the two treatment arms.

Conclusion: Patients with mild-to-moderate hypertension have a beneficial effect from 6-month antihypertensive treatment on diastolic longitudinal left ventricular function; effects are significant with nebivolol, but not with Metoprolol

3 Marazzi G, Iellamo F, Volterrani M, Caminiti G, Madonna M, et al. Comparison of effectiveness of carvedilol versus bisoprolol for prevention of postdischarge atrial fibrillation after coronary artery bypass grafting in patients with heart failure. Am J Cardiol 2011;107(2):215-9.

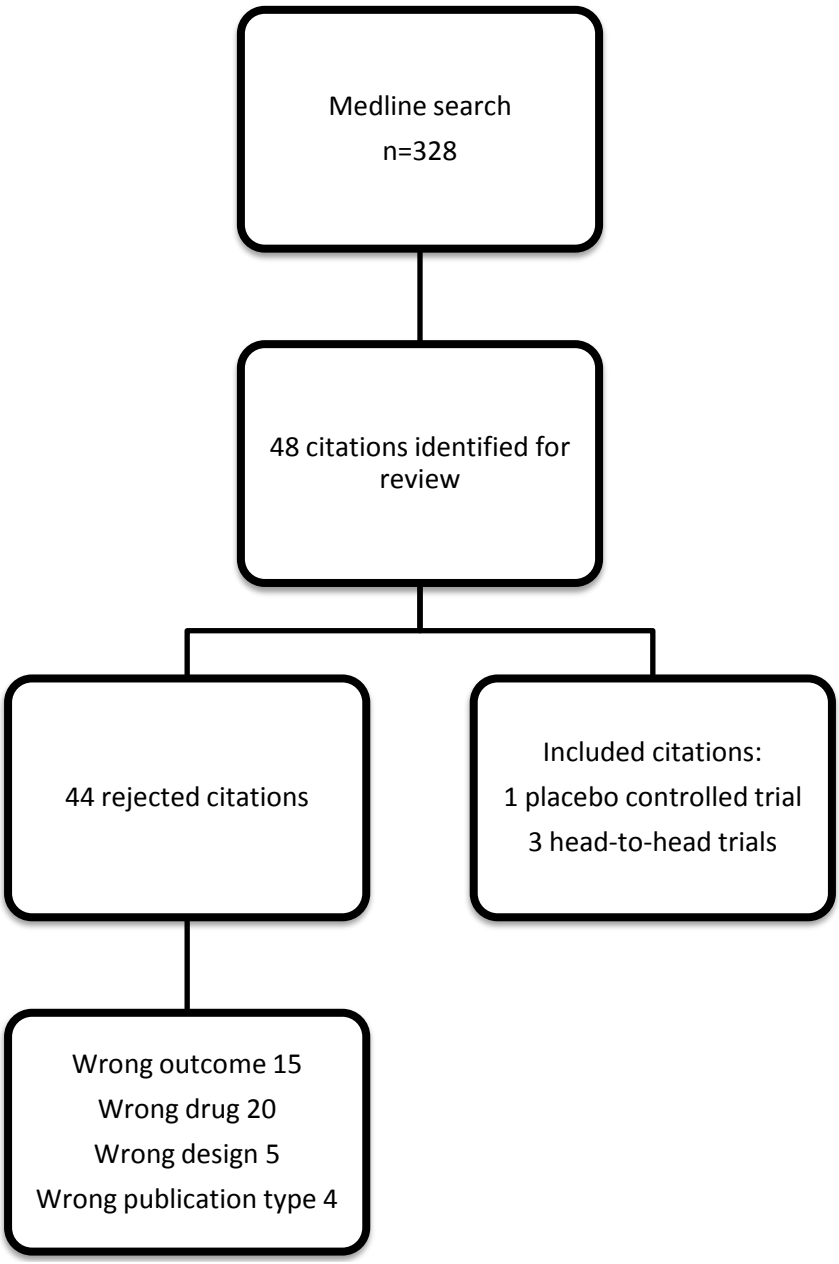
Atrial fibrillation (AF) occurs frequently soon after coronary artery bypass grafting (CABG) and often results in increased mortality and morbidity, particularly in patients with heart failure. New-onset AF is also a common event in the early period after discharge from a cardiac surgery clinic. Current guidelines recommend β blockers as first-line medication for the prevention of AF after CABG. In this prospective study, we investigated the effectiveness of the highly selective β1 receptor antagonist bisoprolol compared to the less selective β blocker carvedilol in preventing postdischarge AF after CABG in patients with decreased left ventricular function. Three hundred twenty patients (231 men, 89 women, mean age 66 ± 10 years) with ejection fraction <40% who underwent CABG and were then referred to an in-hospital cardiac rehabilitation program were randomized to receive bisoprolol (n = 160) or carvedilol (n = 160) starting 4 to 5 days after surgery. Bisoprolol was started at 1.25 mg 1 time/day and carvedilol was started 3.125 mg 2 times/day. All patients underwent continuous telemetric electrocardiographic monitoring for 5 days after entry in the study and thereafter 2 times/day routinely up to hospital discharge. During follow-up, 23 patients (14.6%) in the bisoprolol group and 37 patients (23%) in the carvedilol group developed AF (relative risk 0.6, confidence interval 0.4 to 0.9, p = 0.032). Twenty-six percent of all AF episodes were asymptomatic. At the 4-week outpatient visit, those in the bisoprolol group showed a significantly greater decrease in heart rate, being in sinus rhythm or AF (-15.6 ± 3 vs -9.4 ± 3 beats/min, p = 0.021), whereas changes in systolic and diastolic blood pressures did not differ significantly. In conclusion, bisoprolol is more effective than carvedilol in decreasing the incidence of postdischarge AF after CABG in patients with decreased left ventricular function.

4 Marques F, De Castro RBP, Nobre F, Pintya AO, Gallo Jr. L, et al. Replacement of carvedilol for propranolol in patients with heart failure. Arq Bras Cardiol 2010;95(1):107-14.

Background: Large clinical trials using the beta-blockers carvedilol, metoprolol, bisoprolol and nebivolol have demonstrated improvement of survival and symptoms in patients with heart failure. Despite the lack of scientific evidence, it is plausible that their beneficial effects are extensible to other beta-blockers.
Objective: To evaluate the impact of the replacement of carvedilol for propranolol on left ventricular function, functional capacity, quality of life, pressure levels, and cardiac autonomic control in patients with heart failure.
Methods: Twenty nine patients receiving optimized drug therapy including maximum tolerated doses of carvedilol were divided into two groups: replacement of carvedilol for propranolol (n = 15) and continued carvedilol (n = 14). At baseline and 6 months later, clinical and laboratorial assessments were carried out with radionuclide ventriculography, echocardiography, Minnesota questionnaire, walk test, APBM and Holter monitoring.
Results: The clinical and demographic characteristics were similar in the two groups at baseline. Individualized propranolol dose adjustment ensured a similar degree of beta-blockade, as assessed by resting heart rate and chronotropic reserve. The mean propranolol dose used was 109 ± 43 mg/day. Only one patient presented with intolerance to propranolol, thus carvedilol was reintroduced. One death was recorded in group propranolol.

Ejection fraction significantly increased in the propranolol group. No significant change was observed in the other cardiovascular variables after beta-blocker replacement.
Conclusion: Our results indicate that replacement of carvedilol for propranolol in patients with heart failure is not associated with deterioration of the ejection fraction, functional capacity, quality of life, and other cardiovascular variables related to autonomic and blood pressure control.

Appendix B


Medline search
n=328
48 citations identified for review
44 rejected citations
Included citations:
1 placebo controlled trial
3 head-to-head trials
Wrong outcome 15
Wrong drug 20
Wrong design 5
Wrong publication type 4

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Month/Year of Review: January 2012
Date of Last Review: 2005
PDL Class: Calcium Channel Blockers (CCB)
Source Document: DERP Report

Current Preferred Agents:
Dihydropyridines:
amlodipine
nicardipine
nifedipine ER 24
nifedipine ER SA

Non-dihydropyridines:
diltiazem SR 24 HR
diltiazem ER
diltiazem HCL
verapamil HCL
verapamil HCL 24H

Current Non-Preferred Agents:
felodipine
isradapine
nisoldipine
Nimotop (nimodipine)

Previous Recommendations:

1. The current evidence does not allow for comparisons of CCBs for the treatment of hypertension and does not differentiate amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nisoldipine, or verapamil SR for efficacy, adverse effects and in subgroups for the treatment of hypertension. There is no evidence for bepridil and felodipine.
2. The current evidence does not differentiate amlodipine, diltiazem, nicardipine, nifedipine, and nisoldipine for efficacy in the treatment of chronic stable angina. There is no evidence for felodipine and isradipine. No difference in efficacy was found between dihydropyridines and non-dihydropyridines for the treatment of angina.
3. The current evidence does not differentiate between diltiazem or verapamil for efficacy and adverse effects in the treatment of supraventricular arrhythmias and there is no evidence in subgroups of patients.
4. In the setting of CHF (defined as systolic dysfunction with a LVEF of < 45%) there is evidence that amlodipine and felodipine do not decrease survival or cause harm in this patient population, but neither do they improve survival nor decrease nonfatal cardiovascular events. In patients with systolic dysfunction the evidence does not demonstrate differences between amlodipine, felodipine nifedipine and nisoldipine on symptoms and exercise tolerance.

PA Criteria/QL: Patient must have a covered ICD9 diagnosis.

Background:

Since the DERP report and OHP review of the CCB medications in 2005 there have been 3 DERP CCB class scans conducted in 2006, 2007, and 2009. Based on a defined search criteria a total of 40 potentially relevant trials were identified in those 3 scans (Appendix B - D). The majority of these were identified in the first year following the DERP report. New drugs, indications, and safety alerts found in these scans (2006-2009) since the 2005 report are summarized as follows:

New drugs:

2006 scan
Bepridil discontinued due to ventricular arrhythmias

2009 scan
FDA approved a change in the formulation of extended-release nisoldipine to lower the strengths and replace all current tablets with new lower, bioequivalent strengths.

New FDA Indications:

2006 scan
Amlodipine indicated for use in patients with angiographically documented coronary artery disease– expanded population

New FDA safety alerts:

2007 scan
New information was added to the Precautions section for 4 CCBs:

Cardizem LA (diltiazem hydrochloride) Extended Release Tablets	Drug interactions : Bispirone, Quinidine, Buspirone
Tiazac (diltiazem hcl) ER	Drug Interactions: Bispirone , Quinidine Buspirone: Drug Drug Interactions :
Verelan PM (verapamil hydrochloride) Extended-Release Capsules Controlled Onset	Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class of antibiotics

Methods:

Search Strategy
A search was conducted to identify newly published high quality systematic reviews, new randomized controlled trials, new FDA approved drugs, indications, and safety alerts since the last DERP update scan (2009) was conducted. A MEDLINE OVID search was conducted using the following search terms: Amlodipine, diltiazem, felodipine, nicardipine, nisoldipine, verapamil, bepridil, isradipine, nifedipine, angina pectoris, supreventricular tachycardia, hypertension, heart failure.

The following limitations were used for the search:
All controlled clinical trials or randomized controlled trials
English language
Humans
2010-present

Results:

The MEDLINE search retrieved 217 full citations. These were reviewed for inclusion by evaluating citations and abstracts for head to head trials of CCB's evaluating outcomes of interest. 6 new studies were included and are listed in Appendix A. This includes only 1 head to head trial that compared two CCB's, Nifedipine CR and Diltiazem R in vasopastic angina.

The search of the Cochrane, AHRQ, DERP, and VA/DoD websites did not identify any relevant new systematic reviews.

The FDA website was reviewed for new FDA approved drugs, indications, and safety alerts.

New FDA-approved drugs:
Procardia XL (nifedipine gastrointestinal therapeutic system (GITS)) – once-a-day controlled-release tablet

New FDA Indications:
None identified.

New FDA safety alerts:
None identified.

New Systematic Reviews:
None identified.

Appendix A: New literature from current scan

1. Ferdinand KC, Pool J, et al. Peripheral and central blood pressure responses of combination aliskiren/hydrochlorothiazide and amlodipine monotherapy in African American patients with stage 2 hypertension: the ATLAAST trial. J Clin Hypertens 2011 May;13(5):366-75

Objectives: Evaluate efficacy of antihypertneisve agents on central blood pressure in African Americans.
Design: 8-week double-blind, randomized study of African American patients with stage 2 hypertension that compared brachial and central BP responses to combination aliskiren/HCTZ and amlodipine monotherapy.
Results: Mean seated systolic BP reductions from baseline was similar with both treatments (-28.6 mm Hg with aliskiren/HCTZ vs -28.2 mm Hg with amlodipine). In the substudy, significantly greater reductions in central systolic BP was observed with aliskiren/HCTZ vs amlodipine (-30.1 mm Hg vs -21.2; P=.031), although 24-hour mean ambulatory BP reductions between the two groups were similar.
Conclusions: Central pressure is considered an important risk factor in African Americans, and these findings may suggest a new treatment option for these patients.

2. Saruta, T., K. Hayashi, et al. (2009). "Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: subanalysis of the CASE-J Study." Hypertension Research - Clinical & Experimental **32**(6): 505-12.

Objectives: Examine the effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease (CKD) using the data from the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial.
Design: CKD was defined as proteinuria and/or decreased GFR (<60 ml per min per 1.73 m(2)) at enrollment. Among 2720 subjects with CKD, there were 1376 and 1344 patients in the candesartan and the amlodipine group, respectively.
Results: During a 3.2-year follow-up, cardiovascular event rate did not differ in the two groups (7.2% for candesartan and 7.6% for amlodipine). In the subgroup analysis based on the CKD stage, there were no significant differences in the incidence rates of cardiovascular events between the two groups in stages 1+2 and 3 CKD. In stage 4 CKD, however, candesartan reduced the incidence of cardiovascular events (55% risk reduction), particularly of renal events (81% risk reduction), compared with amlodipine. Furthermore, composite cardiovascular events were increased as the CKD stage progressed, and this effect was exaggerated in the presence of proteinuria. Finally, the new onset of diabetes was less in the candesartan-based regimen in stage 3 CKD.
Conclusions: candesartan protected hypertensive patients with CKD more potently against renal events, particularly in moderately-to-severely impaired CKD. Furthermore, candesartan prevented a new onset of diabetes in CKD, which would be favorable for the long-term management of CKD

3. Higuma, T., Oikawa, K., Kato, T., Mori, Y., Kudo, T., Yamamoto T., et al. (2010). Comparison of the effects of long-acting nifedipine CR and diltiazem R in patients with vasospastic angina: Aomori coronary spastic angina study. *Journal of Cardiology, 56*(3), 354-60.

Objectives: Compare the efficacy of once-daily administration of nifedipine CR 40 mg (N) with that of twice-daily diltiazem R 100mg (D) in patients with vasospastic angina (VSA) registered in 8 cardiovascular institutes in Aomori Prefecture.

Design: VSA was diagnosed by the ischemic ST segment changes during chest pain attacks at rest and/or acetylcholine induction test done during coronary angiography. Thirty-seven patients were randomly allocated to either the N (n=20) or D group (n=17). The number of symptomatic attacks and amount of short-acting nitrate use were examined based on data in diaries written by the patients.
Results: There were no significant differences in the baseline characteristics between the two groups. The mean number (median number) of attacks per week was significantly decreased in the N group from 2.56 (2.0) at baseline to 0.41 (0.0) after 4 weeks of treatment, to 0.24 (0.0) after 8 weeks, and to 0.36 (0.0) after 12 weeks (all $p<0.05$ vs. baseline). It was also decreased in D group from 2.71 (2.0) at baseline to 0.55 (0.0) after 4 weeks, to 0.32 (0.0) after 8 weeks, and to 0.27 (0.0) after 12 weeks (all $p<0.05$ vs. baseline). The numbers of attacks before and after treatment were comparable between N and D groups. In one patient in each of the N and D groups, the allocated drug was crossed over to the other due to recurrence of the attacks. One patient in each group experienced adverse effects and the drug was changed to the other.
Conclusions: Once-daily administration of nifedipine CR was as effective as twice-daily diltiazem R in the prevention of VSA attacks

4. Chrysant, S.G., Lee, J., Melino, M., Karki, S., & Heyrman, R. (2010). Efficacy and tolerability of amlodipine plus olmesartan medoxomil in patients with difficult-to-treat hypertension. *Journal of Human Hypertension, 24*(11), 730-8.

Objectives: Hypertension is particularly prevalent in patients aged ≥65 years, those with a body mass index ≥30 kg m(-2), Blacks and those with type II diabetes. Here we report a prespecified secondary analysis of the efficacy of amlodipine (10 mg day(-1)), olmesartan medoxomil (40 mg day(-1)), a combination of the two and placebo in these subgroups.
Design: Patients were randomized to treatment for 8 weeks. The primary efficacy endpoint was the change from baseline in mean seated diastolic blood pressure (DBP). Secondary efficacy endpoints included the change from baseline in mean seated systolic BP (SBP), proportions of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg in patients with diabetes), and the number and percentage of patients achieving a range of BP targets. Safety and tolerability of amlodipine 5 and 10 mg, olmesartan medoxomil 10, 20 and 40 mg, and all possible combinations of the two were also assessed.
Results: For each prespecified subgroup, all active treatments resulted in significant BP reductions from baseline ($P<0.05$). The antihypertensive effect of the combination of amlodipine+olmesartan medoxomil was generally greater than the constituent amlodipine or olmesartan medoxomil monotherapies, regardless of subgroup. In general, more patients receiving combination therapy achieved BP goal than those treated with monotherapies. The safety and tolerability of combinations were similar to monotherapies across the subgroups.
Conclusions: These results suggest that the combination of amlodipine+olmesartan medoxomil provides a safe and effective option for the treatment of hypertension in challenging patient populations.

5. Meredith, P.A., & Elliott, H.L. (2010). Benefits of nifedipine GITS in stable coronary artery disease: Further analysis of the "ACTION" database. *Advances in Therapy, 27*(5), 297-306.

Objectives: Retrospective analyses of specific subgroups of patients from the database of the ACTION study have evaluated the effectiveness of a nifedipine gastrointestinal therapeutic system (GITS) on clinical outcomes. These subgroups included those patients receiving: 1) full "optimal" therapy at baseline; 2) full "optimal" therapy at baseline but excluding renin angiotensin system (RAS)-blocking drugs; 3) treatment with nifedipine GITS who were not treated with RAS blockers versus those treated with RAS blockers but not nifedipine GITS

Design: Analyses were performed on an intention-to-treat basis. Treatment groups were compared by log-rank test without adjustment for covariates. Hazard ratios with 95% confidence intervals were obtained using Cox proportional hazards models with treatment allocation as the only covariate.
Results: 2461 patients randomized in ACTION were receiving optimal therapy (beta blockers, nitrates, aspirin, statins) excluding RAS blockers at baseline. There were reductions associated with nifedipine GITS compared with placebo in all prespecified endpoints but statistical significance was only achieved for debilitating stroke (48%; P<0.02) and coronary angiography (14%; P<0.05). These benefits were paralleled by a -4.1 and -2.8 mmHg difference between the groups for systolic and diastolic blood pressure, respectively. Patients randomized to nifedipine GITS but no RAS blockers (n=2966) when compared to those receiving RAS blockers but no nifedipine GITS (n=880) had highly statistically significant reductions in cardiovascular events (22%), new-onset heart failure (53%), and debilitating stroke (45%). However, the groups differed in their baseline characteristics..
Conclusions: Addition of nifedipine GITS to the treatment regimen of selected patient groups with symptomatic coronary artery disease results in a significant reduction of cardiovascular morbidity. While the interpretation of these subgroup analyses must obviously be cautious, there is a clear message relating to "best practice" treatment of angina, which suggests that "reliance" on RAS blockade may be misplaced and greater attention should be directed towards control of blood pressure

6. Brown MJ. McInnes GT. Papst CC. Zhang J. MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet. 377(9762):312-20, 2011 Jan 22

Objectives: Test whether a combination of aliskiren and amlodipine is superior to each monotherapy in early control of blood pressure without excess of adverse events, and if initial control by monotherapy impairs subsequent control by combination therapy.
Design: Double-blind, randomized, parallel-group, superiority trial at 146 care sites in ten countries, with enrolment from Nov 28, 2008, to July 15, 2009. Patients eligible for enrolment had essential hypertension, were aged 18 years or older, and had systolic blood pressure between 150 and 180 mm Hg. Patients were randomly assigned (1:1:2) to treatment with 150 mg aliskiren plus placebo, 5 mg amlodipine plus placebo, or 150 mg aliskiren plus 5 mg amlodipine. Random assignment was through a central interactive voice response system and treatment allocation was masked from the patients. From 16-32 weeks, all patients received combination therapy with 300 mg aliskiren plus 10 mg amlodipine. Our primary endpoints, assessed on an intention-to-treat basis (ie, in patients who received the allocated treatment), were the adjusted mean reduction in systolic blood pressure from baseline over 8 to 24 weeks, and then the final reduction at 24 weeks
Results: 318 patients were randomly assigned to aliskiren, 316 to amlodipine, and 620 to aliskiren plus amlodipine. 315 patients initially allocated to aliskiren, 315 allocated to amlodipine, and 617 allocated to aliskiren plus amlodipine were available for analysis. Patients given initial combination therapy had a 6·5 mm Hg (95% CI 5·3 to 7·7) greater reduction in mean systolic blood pressure than the monotherapy groups (p<0·0001). At 24 weeks, when all patients were on combination treatment, the difference was 1·4 mm Hg (95% CI -0·05 to 2·9; p=0·059). Adverse events caused withdrawal of 85 patients (14%) from the initial aliskiren plus amlodipine group, 45 (14%) from the aliskiren group, and 58 (18%) from the amlodipine group. Adverse events were peripheral oedema, hypotension, or orthostatic hypotension
Conclusions: Routine initial reduction in blood pressure with a combination such as aliskiren plus amlodipine can be recommended.

Appendix B: New literature from scan #3 (13)

1. Jamerson, K., M. A. Weber, et al. (2008). "Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients.[see comment]." New England Journal of Medicine **359**(23): 2417-28.

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