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Class Update with New Drug Evaluation: Long-Acting Opioids

Month/Year of Review: March 2015

Date of Last Review: March 2014
Source Document: OSU College of Pharmacy
Brand Name (Manufacturer): Purdue Pharma
Purdue Pharma

New Drugs: Hydrocodone extended release (Hysingla ER®)
Oxycodone/naloxone ER (Targiniq ER®)
Dossier Received: Yes
No

Current Status of PDL Class:

- Preferred Agents: FENTANYL ER TRANSDERMAL FILM (DURAGESIC®), MORPHINE SULFATE ER (MS CONTIN®)
- Non-preferred Agents: BUPRENORPHINE ER TRANSDERMAL FILM (BUTRANS®), HYDROMORPHONE ER (EXALGO®), LEVORPHANOL, METHADONE, MORPHINE SULFATE ER (AVINZA®, KADIAN®), MORPHINE SULFATE/NALTRESONE ER (EMBEDA®), OXYCODONE ER (OXYCONTIN®), OXYMORPHINE ER (OPANA ER®), TAPENTADOL ER (NUCYNTA®), TRAMDOL ER (ULTRAM ER®, CONZIP®), HYDROCODONE ER (ZOHYDRO ER®)

Research Questions:

- Is there any new comparative efficacy and effectiveness evidence of long-acting opioids (LAOs)?
- Is there any new comparative evidence of a meaningful difference in harms of LAOs?
- Is there any evidence that hydrocodone extended release (ER) or oxycodone/naloxone ER are more effective or safer than other LAOs?
- Are there subpopulations of patients for which one LAO medication or formulation is more effective or associated with fewer adverse effects?

Conclusions and Recommendations:

- There is low quality evidence of no clinically meaningful change in pain with hydrocodone ER compared to placebo, as rated on an 11-point pain-intensity numeric rating scale (difference in mean change from baseline -0.53; 95% CI -0.88 to -0.18, p-value 0.0016).[1,2]
- There is low quality evidence of no clinically meaningful change in pain with oxycodone/naloxone ER compared to placebo, as rated on an 11-point pain-intensity numeric rating scale (4.2 versus 3.7; 95% CI 0.1 to 0.8; p-value 0.006).[1,3]
- There is insufficient evidence to establish differences in effectiveness of hydrocodone ER (Hysingla®) or oxycodone/naloxone ER (Targiniq®) versus other LAOs.
- There is insufficient evidence to establish differences in safety of hydrocodone ER (Hysingla®) or oxycodone/naloxone ER (Targiniq®) versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER or oxycodone/naloxone ER from other LAOs.
- Maintain hydrocodone ER and oxycodone/naloxone ER as non-preferred and compare costs in executive session.

Author: Date:

Previous Conclusions and Recommendations:

- There is insufficient comparative evidence to establish differences in effectiveness of hydrocodone ER (Zohydro® ER) versus the other LAOs.
- There is insufficient comparative evidence to establish differences in safety of hydrocodone ER versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER from the other LAOs.
- Maintain hydrocodone ER as non-preferred and evaluate comparative costs in executive session.

PA Criteria:
There is a maximum dose prior authorization (PA) required for doses greater than 120 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20 mg per day when prescribed for pain. Methadone for addiction treatment is covered via professional claims. See Appendix 1.

Background:
Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing, is common. Up to one-third of adults report chronic pain and it is a major cause of decreased quality of life and disability. Despite limited evidence showing long-term benefits, opioids are often used to treat chronic pain. [4] Using long acting opioids (LAOs) for cancer or end of life pain is widely accepted but treating chronic non-cancer pain with opioid therapy is more controversial.[4] Many pain guidelines advocate the use of LAO for chronic non-cancer pain despite limitations in evidence, escalating use, abuse and potential for life-threatening adverse effect. The Veterans Affairs/ Department of Defense Guidelines state that there is good evidence that LAO are effective for continuous pain.[5]

An Agency for Healthcare Research and Quality (AHRQ) class review on using LAOs for non-cancer pain cite that there is no clear evidence that a specific opioid has demonstrated superior efficacy or safety over another. [4] 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 or more effective as initial therapy. Although opioids are viewed as having no maximum dose, guidelines recommend not exceeding 200 mg/day of oral morphine, or equivalent, in patients with chronic non-cancer pain.[6,7]

A variety of patient-reported pain scales are used to assess pain during clinical trials. Pain intensity is frequently measured on an 11-point pain intensity numerical rating scale (NRS), where 0 is no pain and 10 is worst possible pain. A change of -1.74 points and percent change score of -27.9% were best associated with a clinically important improvement using a NRS scale.[1]

Methods:
The DERP Scan[8] was used to identify any new comparative research that has emerged since the last P&T review.

Systematic Reviews:

One new comparative effectiveness review from the AHRQ was identified.[4] This review required follow-up of greater than one year for most outcomes. Due to imprecision and methodological shortcoming, the strength of evidence was rated no higher than low with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing (strength of evidence: moderate). No study evaluated effects of long-term opioid therapy versus no therapy. Compared with nonuse, long-term opioid therapy was associated with increased risk of abuse (one cohort study), overdose (one cohort study), fracture (two observational studies), myocardial infarction (two observational studies) and markers of sexual dysfunction (one cross-sectional study). One cohort study found methadone associated with lower risk of mortality than long-acting morphine in a Veterans Affairs population (HR 0.56, 95% Confidence Interval 0.51 to 0.62). Evidence was insufficient to evaluate benefits and harms of long-term opioid therapy in high-risk patients or in other subgroups.

New Guidelines:

American Pain Society: Methadone Safety (April 2014):

- Patient Assessment and Selection
    - Clinicians should perform an individualized medical and behavioral risk evaluation to assess the risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile (strong recommendation, low-quality evidence)
- Patient Education and Counseling
    - Clinicians should educate and counsel patients prior to the first prescription of methadone about the indications for treatment and goals of therapy, availability of alternative therapies, and specific plans for monitoring therapy, adjusting doses, potential adverse effects, and methods for reducing the potential adverse effects and managing them (strong recommendation, low-quality evidence)
- Baseline Electrocardiograms (ECG)
    - Patients should have a baseline ECG prior to initiation of methadone in patients with risk factors for QTc interval prolongation, any prior ECG demonstrating a QTc >450 ms, or a history suggestive of prior ventricular arrhythmia (strong recommendation, low-quality evidence)
    - Consider obtaining and ECG prior to initiation of methadone in patients not known to be at higher risk of QTc prolongation (weak recommendation, low-quality evidence)
- Initiation of Methadone
    - Clinicians should initiate methadone at low doses individualized based on the indication for treatment and prior opioid exposure status, titrate doses slowly and monitor patients for sedation (strong recommendation, moderate-quality evidence)
    - Clinicians should consider those patients previously prescribed methadone, but who have not currently taken opioids for 1 to 2 weeks, opioid naïve for the purpose of methadone reinitiation (strong recommendation, low-quality evidence)
- Follow-up Electrocardiograms
    - For patients prescribed methadone, clinicians should preform follow-up ECGs based on baseline ECG findings, methadone dose changes, and other risk factors for QTc interval prolongation strong recommendation, low-quality evidence)
    - Methadone-treated adults with a QTc interval ≥500 ms should be switched to an alternative opioid or immediately reduce the methadone dose. (strong recommendation, low-quality evidence)
    - Clinicians should consider switching methadone-treated adults with a QTc interval ≥450 but <500 to an alternative opioid or reduce the methadone dose. Inpatients who cannot be switched, the clinician should discuss the risks of continued methadone with patients (strong recommendation, low-quality evidence)
    - In all cases where the QTc interval is >450 ms, the reversible causes of QTc prolongation should be corrected and the ECG should be repeated after the methadone dose has been decreased (strong recommendation, low-quality evidence)

- Monitoring and Managing Adverse Events
    - Patients receiving methadone should be monitored for common opioid adverse effects and toxicities and that adverse effects management be considered part of routine therapy (strong recommendation, moderate-quality evidence)
    - Face-to-face or phone assessments with patients should be conducted within 3 to 5 days after initiating methadone to assess adverse event. These assessments should be repeated within 3 to 5 days of each dose increase (strong recommendation, low-quality evidence)
- Urine Drug Testing
    - Clinicians should obtain urine drug screens prior to initiating methadone and at regular intervals in patients prescribed methadone for opioid addiction (strong recommendation, low-quality evidence)
    - Patients prescribed methadone for chronic pain who have risk factors for drug abuse should undergo urine drug testing prior to initiating methadone and at regular intervals thereafter; clinicians should consider urine drug testing in all patients regardless of assessed risk status (strong recommendation, low-quality evidence)
- Medication Interactions
    - Clinicians should use methadone with care in patients using concomitant medications with potentially additive side effects or pharmacokinetic or pharmacodynamics interactions with methadone (strong recommendation, low-quality evidence)
- Methadone Use In Pregnancy
    - Neonates born to mothers receiving methadone for neonatal abstinence syndrome should be monitored and treated when neonatal abstinence syndrome is present (strong recommendation, moderate-quality evidence)

New Safety Alerts:

Hydrocodone ER (Zohydro): Two black boxed warnings were issued. The first was a warning that prolonged use may result in neonatal opioid withdrawal syndrome and requires management according to protocols developed by neonatology experts. The second is that concomitant use of hydrocodone ER with all cytochrome P450 3A4 inhibitors or inducers as inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression, and discontinuation of a concomitantly used inducer may result in an increased hydrocodone plasma concentration. [8]

All extended release LAOs had a black box warning added to warn of[8]:

- The potential of addiction, abuse and misuse, which can lead to overdose and death.
- Serious, life-threatening, or fatal respiratory depression following dose increase or misuse of formulations (ie, chewing, crushing or dissolving a formulation which could cause rapid release and absorption).
- Neonatal opioid withdrawal syndrome with prolonged use of the drug during pregnancy.
- Interaction with alcohol which could cause increased plasma levels and a potentially fatal overdose of the opioid.

Risk Evaluation and Mitigation Strategies (REMS) are in place for LAOs to reduce these serious adverse events.

New Formulations or Indications:

None

Randomized Controlled Trials:

Eighty-two potentially relevant citations were evaluated from the literature search. Of these, there were 5 publications of 4 potentially relevant new drugs which are briefly described in the table below. [8] Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Lowenstein, et al.[9]	Oxycodone ER vs oxycodone/naloxone ER	Adults with moderate-to-severe non-cancer pain	Improvement in Bowl Function Index (BFI) at 4 weeks	Oxycodone/naloxone ER showed a significant improvement in BFI compared with those in the oxycodone ER PR group (-14.9; 95% CI: -17.9, -11.9; p<0.0001)
Meissner, et al.[10] Nadstawek, et al.[11]	1. oxycodone ER/placebo 2. oxycodone/naloxone 10mg ER 3. oxycodone/naloxone 20mg ER 4. oxycodone/naloxone 40mg ER	Adults with severe pain	Improvement in Bowl Function Index (BFI) at 4 weeks	At week 4, the 20 mg and 40 mg naloxone groups showed a statistically significant improvement in the BFI compared to placebo (p<0.05). No analyses of change from baseline in BFI or other clinically relevant analyses were reported.
Perlman, et al.[12]	Methadone 1mg/1mL vs hydromorphone tab	Adults requiring dialysis with moderate-to severe pain	Mean percent change in plasma concentration of opioid after dialysis	More change in plasma concentration was seen with hydromorphone (55.1% vs 14.9%) showing a statistically significant difference of 40.2% (95% CI 17.14 to 63.14).
Vondrackova, et. al[13]	1. Oxycodone/naloxone ER 2. Oxycodone ER 3. placebo	Adults with moderate-to-severe low back pain	Time to recurrent pain events	Time was statistically significantly shorter in placebo group compare with oxycodone/naloxone ER (12 to 15 days, p-values between <0.001 and 0.003). There were no statistically significant differences between the oxycodone/naloxone ER and oxycodone ER groups.

NEW DRUG EVALUATIONS:

Hydrocodone ER (Hysingla®)[14,2]

Clinical Efficacy:

The efficacy of hydrocodone ER in moderate to severe chronic low back pain was assessed in one unpublished, 12 week, randomized, double-blind, placebo-controlled trial.[14] The study had an open-label run-in phase of up to 45 days designed to assess patients' qualification for randomization. During this period,

patients started on either 20mg hydrocodone (opioid naïve patients) or a hydrocodone ER dose 25-50% of their incoming opioid daily dose.[2] Patients who demonstrated adequate analgesia (pain reduction of at least 2 points on an 11-point NRS to at least ≤4) and acceptable tolerability qualified for randomization in the 12-week double-blind period.[2] A total of 592 patients qualified for randomization.[2] Patients were randomized to the dose of hydrocodone they were stabilized on in the run-in period or placebo.[2] Patients randomized to placebo were tapered from their run-in dose of hydrocodone ER over the first 14 days of the study. Patients were allowed immediate release oxycodone 5-10 mg every 4-6 hours (up to 30 mg daily) as supplemental analgesic medication.[2] The primary efficacy endpoint was the "average pain over last 24 hours" scores during week 12 using an 11-point NRS, analyzed using Mixed-Effect Model Repeated Measure (MMRM).[2] The least squares mean difference in the primary endpoint compared to placebo was -0.53 (95% CI -0.88 to -0.18, p-value 0.0016).[2] This difference is not clinically significant.[1]

Clinical Safety:
The average daily dose of hydrocodone ER was 56.9mg in the double-blind period.[2] During the run-in period, the incidence of adverse events was 48%.[2] Adverse events that occurred at an incidence of ≥5% during the run-in period included nausea, vomiting, constipation, dizziness, headache and somnolence.[14] Confirmed or suspected diversion by patients overall during the 12-week study period was 4.3%.[14] Less than 1% of patients experienced adverse events associated with opioid withdrawal during the study period. [14]

Pharmacology and Pharmacokinetic Properties[14]:

Parameter	
Mechanism of Action	Opioid receptor agonist, produces analgesia and sedation
Distribution and Protein Binding	Extensive tissue distribution 33%-37%
Excretion	Renal
Half-Life	8 hours
Metabolism	CYP3A4 (primary), CYP2D6, CYP2B6, CYP2C19, other; active metabolite (hydromorphone)

Look-alike / Sound-alike Error Risk Potential: none identified

Oxycodone /Naloxone ER (Targiniq ER®)[3]

Clinical Efficacy:
The efficacy of oxycodone/naloxone ER in patients with uncontrolled moderate to severe chronic low back pain was assessed in one unpublished, 12-week, randomized, double-blind, placebo-controlled trial. [3] A total of 1095 opioid-experienced patients were enrolled in a four week open-label, dose-titration period with oxycodone 5 mg for breakthrough pain. [3] The average age of patients was 54 years, and patients were predominantly Caucasian and female. [3] Only 55% of these patients achieved adequate analgesia and tolerability and were randomized to continue on active drug or switched to placebo. [3] Patients were allowed to

continue taking immediate release oxycodone 5 mg for breakthrough pain, up to twice daily. [3] Overall attrition was high (33%) and more people in the placebo group discontinued due to lack of efficacy versus the treatment group (24% vs 10%). The primary efficacy outcome was average pain over the previous 24 hours at week 12 based on a MMRM analysis. [3] The difference between oxycodone/naloxone ER compared to placebo was statistically significant at 0.5 (4.2 for placebo versus 3.7 for oxycodone/naloxone; 95% CI 0.1 to 0.8; p-value 0.006) using an 11-point numerical pain rating scale. [3] This difference is not clinically significant.[1] No subgroup analyses (gender, age or race) resulted in any major or important differences within groups. [3]

Clinical Safety:
The most common adverse events reported by >5% of patients taking oxycodone/naloxone ER were nausea and vomiting. [3] There were no statistically significant differences in rates of serious adverse events or rates of overall adverse events [3]

Pharmacology and Pharmacokinetic Properties[15]:

Parameter	
Mechanism of Action	Opioid receptor agonist, produces analgesia and sedation (oxycodone) Opioid antagonist that displaces narcotics at opioid receptor sites (naloxone)
Oral Bioavailability	60% to 87% (oxycodone); <3% (naloxone)
Distribution and Protein Binding	45% (oxycodone)
Excretion	Urine and feces (oxycodone and metabolites); urine (naloxone metabolites)
Half-Life	4-5 hours (oxycodone); 4-17 hours (naloxone)
Metabolism	CYP3A4, CYP2D6 (oxycodone); glucuronidation (naloxone)

Look-alike / Sound-alike Error Risk Potential: Targaniq may be confused with Talwin

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Appendix 1:

Opioid Analgesics – High Dose

Goal(s):

- Limit the use of high dose opioid therapy to above-the-line diagnoses that are supported by the medical literature
- Limit the use of non-preferred products
- Promote the safe use of opioids.
  - 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 hypoventilation.
    - This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metabolism of methadone or fentanyl.
  - See Oregon DUR Board newsletter at:
    - http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume11/durv11i2.pdf
    - http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume5/durv5i5.pdf

Initiative:

Long and Short Acting Opioid quantity and dose limits: preferred agents, approved indications, and dose limits.

Length of Authorization:

Up to 6 months

Covered Alternatives:

A list of preferred opioids is available at www.orpdl.org

Requires a PA:

- All non-preferred opioids and preferred opioids exceeding the dose threshold in the table below, not to exceed a Morphine Equivalent Dose (MED) of 120 mg per day.
- Patient with terminal diagnosis, hospice, and metastatic neoplasm (ICD9 = 190xx – 199xx) are exempt from the PA requirements.

-Approved Prior Authorizations may be subject to quantity limits

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	20 mcg/hour (q 7 days)	5mcg/hr patch q 7 days	May increase dose q72 hours patients up to a max of 20 mcg/hr q 7 days. Doses >20 mcg/hr q7days increase risk of QTc prolongation.
Fentanyl Transdermal	50 mcg/hour (q 72 hr)	Use only in opioid-tolerant patients who have been taking ≥ 60 mg MED daily for a week or longer	
Hydromorphone	30mg per 24 hours	2 mg q 4–6 hours	
Methadone	40 mg per 24 hours	2.5-5 mg 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	120 mg per 24 hours	Immediate-release: 10 mg q 4 hours Sustained-release: 15 mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80 mg per 24 hours	Immediate-release: 5 mg q 4–6 hours	See individual product labeling for maximum dosing of combination

		Sustained Release: 10 mg q 12 hours	products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000mg/day x <10 days or 2500 mg/day for 10 days or more)
Oxymorphone	40 mg per 24 hours	Immediate-release: 5–10 mg q 4–6 hours Sustained Release: 10 mg q 12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol**.

Dosing Threshold for select short acting opioids		
Opioid	**Dose threshold**	**Considerations**
Codeine	800 mg/day	
Hydrocodone	120 mg/day	Dosing limits based on combinations (e.g. acetaminophen, ibuprofen) may lower the maximum daily dose

Common indications OHP does not cover:*	**ICD9 Codes**
Disorders of soft tissue (including Fibromyalgia)	*729.0-729.2, 729.31-729.39, 729.4-729.9, V53.02*
Acute and chronic disorders of spine without one of the following neurologic impairments: 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 See Prioritized List of Health Services Guideline Notes 37 and 41	*721-724, except 723.3 739, 839.2, 847*

*Covered diagnoses are dependent on funding levels. A list of currently funded diagnoses can be found at www.oregon.gov/OHA/herc/pages/prioritizedlist.aspx

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9	
2. Is the request for methadone >100 mg?	Yes: Go to #3	No: Go to #5
3. Does the patient have any of the following QTc Risk Factors? • Family history of "long QTc syndrome", syncope, sudden death • Potassium depletion primary or secondary to drug use (i.e. diuretics) • Concurrent use of C34 inhibitors or QTc prolonging drugs (see table below) • Structural heart disease, arrhythmias, syncope	Yes: Go to #4	No: Go to #5

4. Is this new therapy (i.e. no previous prescription for the same drug last month)?	Yes: Pass to RPH; Deny, (Medical Appropriateness) Go over black box warning and offer alternatives (e.g. Fentanyl transdermal, morphine extended release).	No: Pass to RPH, Approve for 30-60 days to allow time to taper or transition to alternative. Direct to DUR Newsletter for assistance. Refer to Rx "Lock-in" Program for evaluation and monitoring.
5. Is the patient being treated for any of the following: a. Oncology pain (ICD-9 338.3) b. Terminal diagnosis (<6 months) c. Hospice care	**Yes**: Go to #6	**No**: Go to #8
6. Is the requested medication a preferred agent?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. Will the prescriber consider a change to a preferred product?	**Yes**: Inform provider of covered alternatives in class.	**No**: Approve for up to 6 months
8. Will the prescriber consider a change to a preferred product not to exceed 120mg MED?	**Yes**: Inform provider of covered alternatives in class.	**No:** Go to #9
9. Is the diagnosis covered by the OHP?	**Yes**: Go to #10	**No:** Pass to RPh, Deny (Not Covered by the OHP) May approve for 30-60 days to allow for tapering
10. Is this new therapy (i.e. no previous prescription for the same drug, same dose last month)?	**Yes**: Go to #11	**No**: Go To #12
11. Does the total daily opioid dose exceed 120 mg MED?	**Yes:** Pass to RPh, Deny (Medical Appropriateness) In general, the total dose of opioid should not exceed 120mg MED Risks substantially increase at doses at or above 100mg MED. Alternatives: Preferred NSAIDs or LAOs @ doses < 120 mg MED.	**No**: Go to #12
12. Has the patient had a recent urinary drug screen (within the past 90 days)?	**Yes**: Go to #13	No: Pass to RPH: Deny (Medical Appropriateness) Recommend Urine Drug Screen

13. Is the patient seeing a single prescribing practice & pharmacy for pain treatment (short and long acting opioids)?	**Yes**: Go To #14	**No:** Approve 30-90 days; Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
14. Does the total daily opioid dose exceed 120mg MED?	**Yes**: Go to #15	**No:** Go to #16
15. 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 LAO or history of drug abuse)?	**Yes: Approve up to 6 months.** **Quantity Limits Apply, e.g.:** 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:** Approve 30-90 days to allow for potential tapering of dose. Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
16. Is the patient concurrently on other long-acting opioids (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, and long-acting oxymorphone)?	**Yes**: Go to #17	**No**: Approve for up to 6 months
17. Is the duplication due to tapering or switching products? The concurrent use of multiple long-acting opioids 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.	**Yes**: Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.	**No: Deny** (Medical Appropriateness) **May approve for taper only.** Refer to Rx Lock-In program for evaluation. If necessary, inform prescriber of provider reconsideration process.

P&T or DUR Board Action: *2/12 (TW), 11/11(KK); 1/09 (KS), 9/09(KK), 12/08 (KK), 3/09*
Revision(s): *6/12, 5/12; 1/12; 1/10*
Initiated: *7/09*

Methadone – New Starts at doses ≥20 mg

Goal(s):

- Promote safe use of methadone upon initiation

Initiative:

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 2.5 mg-5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly

• Use short-acting opioid for breakthrough pain until optimum dose reached.

Length of Authorization:

Up to 6 months

Requires PA:

- Patients initiated on methadone (i.e. no previous claim within 90 days) on a daily dose of >20 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Has patient had a recent urinary drug screen (within the past 90 days)?	Yes: Go to #3	No: Pass to RPH; Deny (Medical Appropriateness) Recommend UDS.
3. Has patient been continuously on opioids other than codeine over the past 90 days?	Yes: Go to #4 Document previous opioid therapy.	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

Approval Criteria		
4. Is the total Morphine Equivalent Dose per Day < 200 mg? Dose Calculator at:		Yes: Pass to RPH; Deny (Medical Appropriateness) Recommend initiate 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
5. Is this patient terminal (<6 months) or admitted to hospice?	Yes: Approve for up to 6 months.	No: Go to #6.
6. Is patient being treated for oncology pain?	Yes: Approve for up to 6 months.	No: Pass to RPH; Deny (Medical Appropriateness)

P&T / DUR Action: *1/12 (KK), 5/11(KK), 3/11(KK)*
Revision(s)
Initiated: *4/12*

Appendix 2: Abstracts of Clinical Trials

Lowenstein O. Leyendecker P. Hopp M. Schutter U. Rogers PD. Uhl R. Bond S. Kremers W. Nichols T. Krain B. Reimer K (2009). Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opinion on Pharmacotherapy. 10(4):531-43, 2009.
BACKGROUND: This randomised, double-blind, double-dummy, parallel-group multicentre study assessed the impact of a total daily dose of 60-80 mg oral oxycodone prolonged-release (PR)/naloxone PR (OXN PR) as fixed-ratio combination for patients with opioid-induced constipation (OIC) having moderate-to-severe, non-malignant pain.
METHODS: During pre-randomisation patients receiving opioids for moderate-to-severe non-malignant pain were converted to oxycodone PR (OXY PR) and titrated to an effective analgesic dose. During randomisation 265 patients on a stable OXY PR dose (60-80 mg/day) and with OIC were included in the full analysis population to receive OXN PR or OXY PR alone. Primary outcome was improvement in symptoms of constipation as measured by the Bowel Function Index (BFI). Secondary/exploratory outcomes examined analgesic efficacy and other bowel function parameters.
RESULTS: After 4 weeks of treatment, patients receiving OXN PR showed a significant improvement in bowel function compared with those in the OXY PR group (-14.9; 95% CI: -17.9, -11.9; p<0.0001) as measured by BFI which was seen after only 1 week of treatment continuing to the end of the study. After 4 weeks of treatment, patients receiving OXN PR had a median number of 3.0 complete spontaneous bowel movements (CSBM) per week compared with only 1.0 for OXY PR alone. Laxative intake was lower in the OXN PR than the OXY PR group. Furthermore, improvements in bowel function were achieved without loss of analgesic efficacy; pain intensity scores were comparable between the groups and consistent for duration of the study. Most frequently reported adverse events were consistent with those reported for opioid analgesics; no new or unexpected adverse reactions attributable to OXN PR used in higher doses were observed.
CONCLUSION: This study shows that the fixed-ratio combination of OXN PR is superior to OXY PR alone in terms of bowel function, while providing effective equivalent analgesia. Unique Identifier: 19243306.

Meissner W. Leyendecker P. Mueller-Lissner S. Nadstawek J. Hopp M. Ruckes C. Wirz S. Fleischer W. Reimer K (2009). A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. European Journal of Pain. 13(1):56-64.
BACKGROUND: Opioid-induced constipation can have a major negative impact on patients' quality of life. This randomised, double-blinded study evaluated the analgesic efficacy of prolonged-release (PR) oral oxycodone when co-administered with PR oral naloxone, and its impact on opioid-induced constipation in patients with severe chronic pain. Another objective was to identify the optimal dose ratio of oxycodone and naloxone.
METHODS: A total of 202 patients with chronic pain (mainly non-cancer related, 2.5% of patients had cancer-related pain) under stable oral oxycodone therapy (40, 60 or 80 mg/day) were randomised to receive 10, 20, 40 mg/day naloxone or placebo. After a 4-week maintenance phase, patients received oxycodone only for 2 weeks. Pain intensity was evaluated using a numerical analogue scale and bowel function was assessed using the bowel function index.
RESULTS: No loss of analgesic efficacy with naloxone was observed. Mean pain intensity scores on randomisation were comparable for placebo, 10mg, 20mg and 40 mg naloxone dose, and remained unchanged during treatment. Bowel function improved with increasing naloxone dose. Naloxone 20mg and 40 mg significantly improved bowel function at the end of the maintenance phase compared with placebo (p<0.05). Overall, the combination was well tolerated, with no unexpected adverse events. There was a trend towards an increased incidence of diarrhoea with higher doses of naloxone. The 2:1 oxycodone/naloxone ratio was identified as the most suitable for further development.
CONCLUSION: Co-administration of PR oral naloxone and PR oral oxycodone is associated with a significant improvement in bowel function compared with PR oral oxycodone alone, with no reduction in the analgesic efficacy of oxycodone. Unique Identifier: 18762438.

Nadstawek J. Leyendecker P. Hopp M. Ruckes C. Wirz S. Fleischer W. Reimer K (2008). Patient assessment of a novel therapeutic approach for the treatment of severe, chronic pain. International Journal of Clinical Practice. 62(8):1159-67.
BACKGROUND AND OBJECTIVES: Opioid-induced constipation can have a major negative impact on patients' quality of life. This randomised clinical trial evaluated patient assessment of the efficacy and tolerability of oral prolonged-release (PR) oxycodone when co-administered with oral naloxone PR.

METHODS: Two hundred and two patients with chronic cancer- or non-cancer-related pain undergoing stable oxycodone PR therapy (40, 60 or 80 mg/day) were randomised to one of four intervention groups: 10, 20 or 40 mg/day naloxone PR or placebo. Following a 4-week maintenance phase, patients were followed-up for 2 weeks in which time they received oxycodone PR only. At the end of the maintenance phase, patients and investigators were asked to assess treatment efficacy and tolerability, as well as preference for the titration or maintenance phase.
RESULTS: Patient and investigator global assessment of efficacy and tolerability improved with increasing naloxone dose. Efficacy was ranked as 'good' or 'very good' by 50.0%, 67.4% and 72.5% of patients in the 10, 20 and 40 mg naloxone PR dose groups, respectively, compared with 43.5% of patients in the placebo group. Patient assessment of tolerability was similar between treatment groups and placebo, being ranked as 'good' or 'very good' by 83.3%, 79.1% and 82.5% of patients in the 10, 20 and 40 mg/day naloxone PR dose groups, respectively, compared with 71.7% of patients in the placebo group. The maintenance treatment phase was preferred by patients in the naloxone groups. A 2 : 1 dose ratio of oxycodone to naloxone was also assessed. Efficacy was ranked as 'good' or 'very good' by 70.4% of patients treated with the 2 : 1 dose ratio compared with 43.5% of patients receiving placebo. Tolerability of the 2 : 1 dose ratio was ranked as being 'good' or 'very good' by 81.5% of patients compared with 71.1% for the placebo group and patients preferred the maintenance phase.
CONCLUSIONS: The co-administration of oral naloxone PR with oxycodone PR improves patient assessment of analgesic opioid therapy for severe chronic pain, in terms of both efficacy and tolerability. Unique Identifier: 18705820.

Perlman R. Giladi H. Brecht K. Ware MA. Hebert TE. Joseph L. Shir Y (2013). Intradialytic clearance of opioids: methadone versus hydromorphone. Pain. 154(12):2794-800.
Opioids are commonly prescribed to patients with chronic pain associated with end-stage renal disease requiring hemodialysis. The stability of opioid analgesia during dialysis may vary among different opioids. No studies to date have corroborated this clinical observation by directly comparing plasma concentrations of different opioids during dialysis. We compared changes in peridialysis plasma concentrations of 2 pharmacokinetically distinct opioids, methadone and hydromorphone (HM). Fourteen dialysis patients with chronic pain received either methadone or HM for at least 2 weeks before beginning the study. Blood samples were obtained immediately before, during, and after hemodialysis in 2 separate dialysis sessions, 1 week apart, and were analyzed for opioid concentrations. Methadone plasma concentrations were more stable during hemodialysis compared to HM: the mean percent change of methadone plasma levels was 14.9% + 8.2% (+ SD) compared with 55.1% + 8.1% in the HM treatment group, a difference of 40.2% (95% confidence interval 17.14 to 63.14). The mean plasma clearance of methadone was 19.9 + 8.5 mL/min (+ SD) compared with 105.7 + 8.3 mL/min for HM, a difference of 85.7 mL/min (95% confidence interval 61.9 to 109.1). There were no differences between the 2 opioid groups in pain scores, side effect profile, and quality of life. Methadone therapy was not associated with an increased rate of adverse events. If confirmed by larger clinical studies, methadone could be considered as one of the opioids of choice in dialysis patients. Unique Identifier: 23973378.

Vondrackova D. Leyendecker P. Meissner W. Hopp M. Szombati I. Hermanns K. Ruckes C. Weber S. Grothe B. Fleischer W. Reimer K (2008). Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. Journal of Pain. 9(12):1144-54.
This randomized, double-blind, placebo- and active-controlled, parallel-group study was designed to demonstrate the superiority of oxycodone in combination with naloxone in a prolonged release (PR) formulation over placebo with respect to analgesic efficacy. The active control group was included for sensitivity and safety analyses, and furthermore to compare the analgesic efficacy and bowel function of oxycodone PR/naloxone PR with oxycodone PR alone. The analgesic efficacy was measured as the time from the initial dose of study medication to multiple pain events (i.e., inadequate analgesia) in patients with moderate to severe chronic low back pain. The full analysis population consisted of 463 patients. The times to recurrent pain events were significantly longer in the oxycodone PR/naloxone PR group compared with placebo (P < .0001-.0003); oxycodone PR/naloxone PR reduced the risk of pain events by 42% (P < .0001; full analysis population). The appearance of pain events was comparable for oxycodone PR/naloxone PR versus oxycodone PR, confirming that the addition of naloxone PR to oxycodone PR in a combination tablet did not negatively affect analgesic efficacy of the opioid. Furthermore, oxycodone PR/naloxone PR offers benefits in terms of an

improvement in bowel function. In a therapeutic area of great unmet need, therefore, the combination tablet of oxycodone PR/naloxone PR offers patients effective analgesia while improving opioid-induced bowel dysfunction. Taken together with the observation that the safety profile of oxycodone PR/naloxone PR is consistent with that expected from other opioid analgesics except opioid-induced constipation, these findings indicate that the addition of naloxone to oxycodone in a PR combination tablet offers improved tolerability. Oxycodone PR/naloxone PR is therefore a promising new treatment approach for the management of chronic pain.
PERSPECTIVE: This study evaluated the analgesic efficacy and safety of the combination of oxycodone PR/naloxone PR in chronic nonmalignant pain. Opioids are often reduced in dosage or even discontinued as a result of impaired bowel function, leading to insufficient pain treatment. Not only does oxycodone PR/naloxone PR demonstrate analgesic efficacy comparable with oxycodone PR, but it also improves opioid-induced bowel dysfunction, and may therefore improve the acceptability of long-term opioid treatment for chronic pain. Unique Identifier: 18708300.