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 Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 31, 2013 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff.

I. CALL TO ORDER
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Membership Report — R. Citron (OSU)
- c. Conflict of Interest Declaration — R. Citron (OSU)
- d. Approval of Agenda and Minutes — B. Origer (Chair)
- e. Department Update — T. Douglass (DMAP)

II. OPERATING PROCEDURES
- a. Updated Document — R. Citron (OSU)
- b. Quality Assessment Tools — K. Ketchum (OSU)
- c. Clinical Procedures — M. Herink (OSU)
- d. Public Comment

III. NEW BUSINESS
- a. FDB Drug File Updates* — T. Williams (OSU)
  1. List of Drugs
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- b. Retisert*
  1. Abbreviated New Drug Evaluation — M. Herink (OSU)
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- c. Overactive Bladder Class Update* — B. Liang (OSU)
  1. Mirabegron (Myrbetriq®) New Drug Evaluation
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- d. Aclidinium Bromide (Tudorza Pressair®)* — B. Fouts (OSU)
  1. New Drug Evaluation
  2. Public Comment
  3. Discussion of clinical recommendations to OHA
- e. Combivent Respimat®* — M. Herink (OSU)
  1. Abbreviated New Drug Evaluation
  2. Public Comment
  3. Discussion of clinical recommendations to OHA

**Agenda items 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. Macrolide Antibiotics
2. Fluoroquinolone Antibiotics
3. GI: PPI's and H2A's
4. Antihistamines
5. Public Comment
6. Discussion of clinical recommendations to OHA

IV. EXECUTIVE SESSION

V. RECONVENE for PUBLIC RECOMMENDATIONS

VI. ADJOURN

**Agenda items 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)*

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

OREGON PHARMACY & THERAPEUTICS COMMITTEE MEMBERSHIP REPORT

First Name	LastName	Title	Position	Date Began	Term Ends	Specialty/Practice Setting	Geography
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	Nurse Practitioner	Portland
Phillip	Levine	PhD	Public	Nov-11	**Dec-15**	Retired	Lake Oswego
Meena	Mital	MD	Physician	Nov-11	Dec-14	Deputy Medical Director	Portland
William	**Nunley**	**MD**	**Physician**	**Nov-12**	**Dec-15**	**Associate Medical Director**	**Portland**
William	Origer	MD	Physician	Nov-11	Dec-14	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-15**	Pharmacy Manager	Silverton

Created on 1/29/2013 12:12:00 PM
Modified on 1/29/2013

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 Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, November 29, 2012 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff.

Members Present: Andris Antoniskis, MD; Tracy Klein, PhD, FNP; Phillip Levine, PhD; William Origer, MD; Cathy Zehrung, RPh
Members Present by Phone: Joshua Bishop, PharmD; David Pass, MD; Stacy Ramirez, PharmD
Staff Present: Roger Citron, RPh; Megan Herink, PharmD, BCPS; Kathy Ketchum, RPh, MPA:HA; Ann Hamer, PharmD, BCPP; Ted Williams, PharmD; Valerie Smith; Richard Holsapple, RPh; Trevor Douglass, DC, MPH, Israel Harden
Staff Present by Phone: Kathy Sentena, PharmD
Audience: Pam Dahl, Digestive Care, Inc.; Brenda Bloom, Regeneron; John Han, Regeneron; Paul Borham, Novo Nordisk; David Baher; Venus Holder, Lilly; Jim Graves, BMS; Alison Little, OHSU; Richard Kosesan; Liz Cleland, OR Society of Med Oncology; Rise Cleland, WA Society of Med Oncology; Annie Ogostoalick, Abbott; Tammi Laclerc, Eisai; Kathryn Munoz, Eisai; Steve Faloon, Otsoka; Jason Parks, ACS CAN; Shane Hall, Purdue; Deborah Wager, Gilead; Lori Hawarth, Bayer; Michelle Besi, Gilead; Barry Benson, Merck; S. Beaty, Med Immune; Shauna Williams, DK Pierce & Associates; Anne Murray, BMS; Paul Nielsen, Med Immune; Jim Hoover, Bayer; Kent Hef, Takeda; Cat Livingston, HERC; Linda Craig, A2; Desiree Allen, Abbott; Clayton Wright, MLMN; Darren Coffman, HERC; Bruce Smith, GSK; Albert Chira, OSU; Courtni Dresser, OMA

I. CALL TO ORDER
a. Dr. Origer called the meeting to order at approximately 1:05pm.
b. Conflict of interest declarations were reviewed; no new conflicts were reported.
c. The minutes from the September 27, 2012 meeting were reviewed.

ACTION: The minutes were approved as is.

II. HERC COVERAGE GUIDANCE
a. Dr. Livingston and presented ADHD draft coverage guidance. Allison Little from OHSU Center for Evidence-based Policy presented public comment received to date.
b. Dr. Livingston presented on therapies with marginal benefit and/or high cost. Darren Kaufman presented public comment received to date.

III. DUR ACTIVITIES
a. Mr. Holsapple presented the ProDUR report.
b. Dr. Williams presented the RetroDUR report.
c. Mr. Citron presented the quarterly utilization reports.

**Agenda items 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)*

d. Dr. Douglass presented the DMAP update.

e. Dr. Sentena presented the Oregon State Drug Review titled *Do Spinosad or Ivermectin Have a Place in Head Lice Eradication?*

f. Dr. Hamer presented on low dose aripiprazole (Ability®) education proposal. Jim Graves from BMS presented public comment.

IV. OLD BUSINESS

a. Dr. Herink presented on Vascular Endothelial Growth Factors (VEGF) Inhibitors recommending pegaptanib be non-preferred, bevacizumab be preferred. John Han from Regeneron Pharma presented public comment. Written public comment was submitted by Andreas K. Lauer, MD from the Casey Eye Institute.

***ACTION:** The Committee approved making pegaptanib non-preferred before Executive Session and approved making bevacizumab preferred after Executive Session.

b. Dr. Herink presented proposed prior authorization changes for Erythropoiesis Stimulating Agents.

***ACTION:** The Committee approved updates to the existing prior authorization criteria.

c. Ms. Ketchum presented follow-up pricing on the Phosphate Binders drug class during Executive Session recommending Renagel® be preferred after a trial of calcium acetate which should also be a preferred product.

***ACTION:** The Committee approved making calcium acetate and Renagel® preferred after Executive Session.

d. Ms. Ketchum presented follow-up pricing on the DPP-4 Inhibitors drug class during Executive Session recommending Januvia® and Janumet® be preferred after trial of metformin and sulfonylurea.

***ACTION:** The Committee approved making Januvia® and Janumet® preferred after Executive Session.

V. NEW BUSINESS

a. Ms. Ketchum presented a drug use evaluation on Physician Administered Drugs recommending:

1) Close any new PAD HCPC codes until reviewed by P&T for appropriateness (PDL class, OHP coverage, etc.)

2) Coordinate coverage of drugs billed via drug claims and medical claims

a. Evaluate feasibility of closure of HCPC codes for self-administered drugs and consider closure of NDCs for clinic administered drugs.

b. Establish a duplicate claim edit across all claims (same patient, same drug, same DOS) where it is appropriate to bill in either program.

c. Phase in the current drug PA requirements for medical claims starting with classes with limited numbers of providers to target education of the PA process (i.e. BONE, EMET, EPO, MS, TIMS)

d. Insure that provider reimbursed amounts are similar in both programs.

3) Work with oncology specialists to develop a management plan using best practices to possibly include the following:

a. Implement PA for National Comprehensive Cancer Network (NCCN) guidelines adherence of high cost/high risk oncology drugs

b. Implement value-based reimbursement of oncology drugs

i. Higher reimbursement margin to providers and no barriers for high value drugs

ii. Limit coverage or limit reimbursement margin for drugs with marginal benefit at higher cost

4) Evaluate use of IU and vaginal ring contraception versus other forms.

5) Consider prior authorization of natalizumab, a drug with limited indications for Multiple Sclerosis and Chron's Disease and a black box warning for risk of progressive multifocal leukoencephalopathy.

6) Follow-up with specific DUEs of immune globulin and musclular blockage drugs.

**Agenda items 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)*

Lori Howarth from Bayer presented public comment.

***ACTION:** The Committee approved all of the PAD recommendations, but would like staff to take small clinics that get PAD drugs through pharmacies and administer to patients into consideration before acting on the 2.a. recommendation.

b. Dr. Herink presented a new drug evaluation on obesity drugs recommending to cover phentermine/topiramate and lorcaserin for funded diagnoses only and since the treatment of obesity with medications is currently an OHP unfunded diagnosis, eliminate current Weight Loss Medications prior authorization criteria. Kathryn Munoz from Eisai presented public comment.

***ACTION:** The Committee approved the recommendations.

c. Dr. Herink presented an abbreviated class update on Benign Prostatic Hypertrophy recommending maintaining one alpha-blocker and one 5-alpha reductase inhibitor as preferred, making tadalafil non-preferred for the treatment of BHP, updating PA criteria for indication of tadalafil for the simultaneous occurrence of BPH and erectile dysfunction, and continue requiring PA in accordance with OHP list of prioritized health services and limit cosmetic use.

***ACTION:** The committee approved no changes to the BPH PDL drug class after Executive Session and approved other recommendations before Executive Session.

d. Dr. Herink presented an abbreviated class review on Pancreatic Enzyme Replacement Products recommending Creon® and rebatable generic lipase/protease/amylase products be preferred. Annie Ogostalick from Abbott presented public comment. Pamela Dahl from Digestive Care Inc. presented public comment.

***ACTION:** The committee approved these recommendations after Executive Session.

e. Dr. Herink presented drug class scans with the following recommendations:

1. Estrogens, recommending Climara® be preferred and grandfather recipients currently on other topical hormone replacement agents for 90 days, Jinteli® and Jevantique® be age restricted to <50yrs to limit use to oral contraception and make Estring® non-preferred as the vaginal hormone replacement. No further research required at this time.

***ACTION:** The committee approved these recommendations after Executive Session.

2. Cephalosporins, recommending no changes to the first or second generation agents, making Suprax®, cefpodoxime and Cedax® suspension non-preferred. No further research required at this time.

***ACTION:** The committee approved these recommendations after Executive Session.

3. Ophthalmic Antibiotic-Steroid Combinations, recommending no changes. No further research required at this time.

***ACTION:** The committee approved these recommendations after Executive Session.

VIII. The meeting was adjourned at approximately 4:30pm.

**Agenda items 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)*

OREGON HEALTH AUTHORITY
DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

OPERATING PROCEDURES
Updated: January 2013

MISSION:
To evaluate available evidence-based research using a transparent process to encourage safe, effective, and financially sustainable drug use policies that maximize access to high value medications for patients served by the Oregon Health Plan and other health care programs under the Oregon Health Authority.

DUTIES:
As defined by Oregon House Bill 2100 the Pharmacy and Therapeutics (P&T) Committee was established to perform functions previously fulfilled by the Drug Use Review Board and Health Resources Commission. Responsibilities of the P&T committee include:

1. Evaluate evidence-based reviews of prescription drug classes or individual drugs to assist in making recommendations to the Oregon Health Authority for drugs to be included on the preferred drug list (PDL).
    a. The Committee may direct a Subcommittee to prepare these reviews.

2. Advise the Oregon Health Authority on administration of Federally mandated Medicaid retrospective and prospective drug use review (DUR) programs which includes recommending utilization controls, prior authorization requirements, quantity limits and other conditions for coverage.

3. Recommendations will be based on evaluation of the available evidence regarding safety, efficacy and value of prescription drugs, as well as the ability of Oregonians to access prescriptions that are appropriate for their clinical conditions.

4. Publish and distribute educational information to prescribers and pharmacists regarding the committee activities and the drug use review programs.

5. Collaborate with the Health Evidence Review Commission (HERC) on topics involving prescription drugs that require further considerations under the purview of the HERC.

AD-HOC EXPERT INVOLVEMENT:

1. A medical expert may be chosen and appointed by the Director of the OHA to provide clinical or treatment expertise in response to a request by the P&T Committee or an interested outside party. The ad-hoc expert must be a licensed physician in Oregon who manages patients who would potentially receive the particular drug(s) and must be approved by the P&T Committee.

2. If an interested outside party requests that an ad-hoc expert be appointed for a particular drug, this request must be made 90 days before the scheduled Committee meeting to ensure adequate time for the appointment process.

3. The medical experts shall have full voting rights with respect to the PDL drugs for which they have been selected and appointed including all utilization controls, prior authorization requirements, review of

confidential pricing information or other conditions for the inclusion of a drug on the PDL. The medical experts may participate but may not vote in any other activities of the committee.

CONDUCT OF MEETINGS:

1. All meetings and notice of meetings will be held in compliance with the Oregon Public Meetings Law.

2. The P&T Committee will elect a Chairperson and Vice Chairperson to conduct the meetings. The Committee shall determine the term of this post. Elections shall be held the first meeting of a calendar year for the following year.

3. Quorum consists of 6 permanent members of the P&T Committee. Quorum is required for any official vote or action to take place throughout a meeting.

4. All official actions must be taken by a public vote. Any recommendation from the Committee requires an affirmative vote of a majority of the Committee members.

5. The committee shall meet in executive session for purposes of reviewing the prescribing or dispensing practices of individual physicians or pharmacists; reviewing profiles of individual patients; and reviewing confidential drug pricing information to inform the recommendations regarding inclusion of drugs on the PMPDP or any preferred drug lists adopted by the OHA.

6. Meetings will be held at least quarterly but the Committee may be asked to convene up to monthly by the call of the director or a majority of the members of the Committee. DUR programs will be the focus of the meeting quarterly.

CONFLICT OF INTEREST POLICY:

The P&T Committee will function in a way that ensures the objectivity and credibility of its recommendations.

1. All potential initial committee members, future applicants, and ad- hoc medical experts selected for individual P&T Committee meetings are subject to the Conflict of Interest disclosure requirements in ORS Chapter 244 and are required to submit a completed disclosure form as part of the appointment process and must update when necessary.

2. All disclosed conflicts will be considered before an offer of appointment is made.

3. If any material conflict of interest is not disclosed by a member of the Committee on his or her application or prior to participation in consideration of an affected drug class or other action of the Committee, that person will not be able to participate in voting decisions of the particular drug class and may be subject to dismissal.
4. Any person providing public testimony will also be required to disclose all conflicts of interest as they pertain to the issue before the Committee including industry funded research.

PUBLIC COMMENT:

1. The P&T Committee meetings will be open to the public

2. The Committee shall provide appropriate opportunity for public testimony at each meeting

    a. Testimony can be submitted in writing or provided in-person

    b. Maximum of 5 minutes per speaker.

        i. Information that is most helpful to the Committee is evidence-based, comparative and limited to new information not previously reviewed by the Committee and relating to dossier information or prepared reviews.
        ii. Oral presentation of the FDA approved label is not helpful information.

    c. Written testimony can be submitted by interested parties for the P&T Committee to consider on agenda items. Written testimony which includes clinical information, such as Dossiers, can be submitted for consideration of inclusion through the public comment link found on the P&T website (http://oregonstate.edu/tools/mailform?to=osupharm.di@oregonstate.edu&recipient=Drug+Use+Research+and+Management). It must be received by staff during the dates provided on the website.

    d. Written documents provided during the scheduled public testimony periods of the P&T meetings will be limited to 2 pages of new information that was not included in previous reviews. Package Inserts (PIs) are not considered new information and only clinically relevant changes made to the PIs should be submitted.

REVIEW STANDARDS AND PREFERRED SOURCES OF EVIDENCE

1. The P&T Committee and department staff will evaluate drug reviews that are based on sound evidence-based research and processes widely accepted by the medical profession.

2. The P&T Committee will rely heavily on high quality systematic reviews and evidence-based guidelines in making its decisions. Clinical judgment will still need to be used by the Committee to determine whether the available evidence is sufficient and compelling enough to affect drug benefit decisions.

3. The following are considered preferred sources of high quality evidence:

    a. OHSU's Drug Effectiveness Review Project (DERP)
    b. VA/DoD Health Information Sharing
    c. Agency for Healthcare Research and Quality (AHRQ)
    d. Canadian Agency for Drugs and Technologies in Health (CADTH)
    e. The Cochrane Collaboration
    f. National Institute for Clinical Excellence (NICE)
    g. Institute for Clinical and Economic Review (ICER)
    h. Published systematic reviews from validated Evidence-Based Medicine sources

4. The following types of evidence are preferred and will be considered if they are of high quality:

    a. Systematic reviews of randomized controlled trials
    b. Individual comparative effectiveness randomized controlled trials (RCTs) evaluating clinically important outcomes
    c. FDA review documents
    d. Guidelines developed using explicit evidence evaluation processes.

5. The following types of literature are considered unreliable sources of evidence and will rarely be reviewed by the P&T Committee:

    a. Case reports, case series
    b. Unpublished studies (posters, abstracts, presentations, non-peer reviewed articles) that do not include sufficient methodological details for quality evaluation, with the exception of FDA review documents.
    c. Individual studies that are poorly conducted, do not appear in peer-reviewed journals, are inferior in design or quality to other relevant literature, or duplicate information in other materials under review
    d. Studies that are not designed to investigate clinically relevant outcomes.

6. Before a review is evaluated at a P&T meeting, a final draft including all acceptable written public comments received during the public comment period shall be made publicly available for a period of a least 30 days.

7. The P&T Committee will consider the overall quality of the evidence available at the time of review and public comments and take one of the following actions:

    a. Accept or reject the review and recommendations as written.
    b. Make edits to the review and recommendations and accept as modified.
    c. Request further work from the staff on the topic.

DRUG REVIEWS:

1. Drug Reviews:

    a. The P&T Committee will review drugs and/or drug classes that have not been previously reviewed for PDL inclusion or PA criteria as the committee sees appropriate and will be prioritized based on:
        i. Potential benefit or risk
        ii. Use or potential use in covered population
        iii. Potential for inappropriate use
        iv. Alternatives available
        v. OHP Coverage based on opportunities for cost savings, to ensure medically appropriate drug use, or address potential safety risks.

    b. The P&T Committee will make a reasonable effort to perform a timely review of new FDA-approved drug products following their market release, when they are a new molecular entity and are candidates for coverage under the pharmacy benefit.

    c. Line Extension and Combination Product policy

i. Line extensions include new strengths and new dosage forms for an existing drug
    1. When a new strength or dosage formulation becomes available for a drug previously reviewed for the PDL and has PA criteria and the new product does not significantly differ from the existing drug based on clinical evaluation, the same utilization restrictions as the existing drug will apply without a full P&T Committee new drug review until the next scheduled Committee review.
    2. If a new formulation becomes available for an existing preferred drug and the new product does significantly differ from the existing medication, has a new indication or significantly differs in cost, the drug will not be preferred until presented to the P&T Committee for an abbreviated review.

ii. When a new combination product becomes available that is a formulation of one or more drugs that have been reviewed for the PDL, where applicable, the product will be designated a non-preferred drug until the P&T Committee review.

d. P&T staff may engage relevant health care professionals with clinical specialty to serve as expert reviewers- in addition to the ad-hoc experts- if it is felt to be needed based on the drug being reviewed.

2. Preferred Drug List Updates:

a. Drugs and drug classes that have previously been reviewed for the PDL will be evaluated and scanned for the need of an update periodically based on new clinically relevant information since the last review.
    i. All drugs and drug classes reviewed for a potential update will be listed on the meeting and agenda and available to the public.

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences

• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.

Author: Date

• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-po licy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf

Author: Date

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

Recent Additions to the First DataBank (FDB) Drug File

Following is a list of agents recently added to the FDB drug file which were not subject to previous PA criteria. In accordance with OAR 410-121-0040(5)(b)

> *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*

these medications require a Prior Authorization to ensure use only for funded conditions.

Week of:	Generic	Brand	FDA Approved Indication(s)	ICD9 Code	HERC Funding Line
11/11/2012	OCRIPLASMIN	Jetrea®	Symptomatic Vitreomacular Adhesion	379.27	686
9/17/2012	LINACLOTIDE	Linzess®	Irritable bowel syndrome	564.1	551
			Chronic idiopathic constipation	564.0	551
12/23/12	Pinazepam	n/a	n/a	n/a	n/a

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Drug Evaluation: Fluocinolone acetonide intravitreal implant (Retisert®)

Month/Year of Review: January 2013
End date of literature search: September 2012
Generic Name: Fluocinolone acetonide intravitreal implant
Brand Name (Manufacturer): Retisert® (Bausch & Lomb)

FDA Approved Indication:
The Fluocinolone ocular implant is a corticosteroid surgically implanted; indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.[1]

Research Questions:
- Is there evidence to support the use of fluocinolone acetonide intravitreal implant over another delivery device and/or standard of care for the treatment of uveitis or other macular edema indications?
- Is there any high quality evidence to support the use of fluocinolone acetonide intravitreal implant over other steroid implant devices?
- Are there certain subpopulations, where corticosteroid intravitreal implants are either more effective or safer than other treatments for uveitis and other macular edema indications?

Conclusions:
- There is low quality evidence that there is no difference in visual acuity outcomes between fluocinolone acetonide intravitreal implant and standard of care with systemic corticosteroids for the treatment of noninfectious uveitis. There is also low quality evidence that fluocinolone intravitreal implant may control inflammation in the eye faster and more frequently than standard of care, although both approaches decrease inflammation.
- There is moderate quality evidence that fluocinolone acetonide intravitreal implant is associated with more ocular adverse events than standard of care, including glaucoma (Hazard Ratio [HR] 4.2, 95% CI 1.82-9.63) and cataracts (HR 4.12, 95% CI 2.2-7.7).
- There is low quality evidence demonstrating potential benefit of fluocinolone acetonide intravitreal implant and dexamethasone implant for the treatment of diabetic macular edema, however significant complications have also been reported. There is insufficient evidence to support the use for diabetic macular edema or other off-label indications.
- There is insufficient evidence directly comparing fluocinolone acetonide intravitreal implant to dexamethasone intravitreal implant for any indications. There are significant differences in indications and administration techniques between the two agents.
- There is moderate quality evidence demonstrating efficacy of dexamethasone intravitreal implant following central retinal vein occlusion.

Recommendations:

- Recommend that the Health Evidence Review Commission evaluate the surgical procedure of the fluocinolone ocular implant for line placement.

Background:

Uveitis is an ocular inflammatory condition that may be related to infection or are non-infective.[2, 3] The standard of care for noninfectious uveitis is local, topical, or oral corticosteroids in combination with immunosuppressive therapy, when indicated.[3] The goal of treatment is to suppress inflammation and achieve remission and protection of visual acuity. Topical corticosteroids penetrate well only into the anterior segment of the eye and are useful in the management of anterior uveitis, but do not adequately penetrate the posterior segment of the eye. Periocular steroids are useful in intermediate uveitis and posterior uveitis. However, many patients need systemic steroids, primarily orally with or without immunosuppressive drug therapy. Treatment guidelines from 2000 and 2005 recommend topical, local, or systemic corticosteroids to control ocular inflammation rapidly. To decrease the risk of serious side effects associated with corticosteroid use, guidelines recommend the addition of immunomodulatory therapy as a steroid-sparing agent if inflammation is not controlled within three months with steroid use (≤10 mg/day of prednisone or equivalent). [3, 4] Intravitreal implants were developed to deliver a continuous concentration of drug over a prolonged period of time and are either biodegradable or nonbiodegradable. Although this continuous release may reduce the need for intravitreal injections or long-term systemic therapy, surgical implantation of the device carries its own risks, and the implant could potentially increase ocular toxicity due to increased corticosteroid concentrations in the eye over a longer duration.

In 2005, the FDA approved the intraocular fluocinolone implant (Retisert®) for chronic, noninfectious uveitis which is a non-biodegradable implant that delivers drug continuously for about 30 months. The fluocinolone implant is surgically implanted by a vitreoretinal surgeon. Approval for noninfectious uveitis was based on two phase III, randomized, double-masked, historically controlled clinical trials demonstrating a clinically and statistically significant difference in the proportion of patients with recurrence of uveitis within 34 weeks post-implantation compared to the proportion with recurrence in the 34 weeks preceding implantation.[5] The fluocinolone implant reduced the rate of recurrence from 62% in the year preceding implantation to 20% in the 0.59-mg group and 41% in the 2.1-mg group post implantation. There was also a significant improvement in visual acuity when compared to the nonimplanted eyes ($p<0.01$). There was no significant difference in the proportion of eyes with deteriorating visual acuity. [5] There was a significant increase in the incidence of cataracts in the implant eyes compared to the nonimplanted eyes (67% vs. 18%, $p<0.01$; RR 3.7, 95% CI 2.7 to 5.2) and 93% of implanted eyes underwent cataract surgery. [5]

In 2009 the dexamethasone ocular implant (Ozurdex®) was approved for macular edema following retinal vein occlusion (RVO), and in 2010 also for the treatment of non-infectious uveitis, affecting the posterior segment of the eye. This implant is biodegradable and releases dexamethasone over about 6 months. The dexamethasone ocular implant can be given as an outpatient procedure, while fluocinolone has to be surgically inserted. The safety and efficacy of the dexamethasone intravitreal implant for the treatment of non-infectious uveitis affecting the posterior segment of the eye was studied in a single, multicenter, masked, randomized 26 week trial.[6] Two hundred and twenty nine subjects were randomized to dexamethasone implant 0.35mg, 0.7mg, or a sham procedure. The primary outcome was the percentage of eyes with a vitreous haze score of 0, which represents no inflammation, at week eight of the trial. Outcome investigators and patients were masked, while treatment investigators were unmasked in order to perform the implant placement. The percentage of eyes with a vitreous haze score of 0 at week eight was significantly greater in both the 0.7-mg (47%; $p<0.001$) and the 0.35 mg group (36%; $p<0.001$) than the sham group (12%).[6] There were also significantly more eyes with improved visual acuity in the dexamethasone implant groups than the sham group. The authors concluded that in this study a single dose of the dexamethasone implant was well tolerated and produced significant improvements in intraocular inflammation and visual acuity that persisted for six months. In addition, it was noted that the 0.7 mg implant demonstrated greater efficacy than the 0.35 implant, with similar safety. [6]

Author: M. Herink, Pharm.D.

Research is also being conducted on evaluating the safety and efficacy of fluocinolone acetonide intravitreal implant as off-label use for the treatment of diabetic macular edema (DME). Previous treatment approaches for DME include laser photocoagulation, intravitreal steroid injections, vitrectomy, and vascular endothelial growth factor (VEGF) inhibitors. Laser photocoagulation has historically been the gold standard but has not been successful in improving vision, only preserving it. Intravitreal steroids are not commonly used due to the risk of elevated intraocular pressure and cataracts.[7] There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with DME relative to laser treatment and sham injection, with similar improvements across agents.[8] An additional fluocinolone intravitreal implant (Iluvien®) has been submitted to the FDA for the indication of DME but has not yet been approved.

Systematic Reviews

National Institute for Health and Clinical Excellence

A 2011 technology appraisal was published in 2011 by the National Institute for Health and Clinical Excellence (NICE) on dexamethasone implant for macular edema secondary to retinal vein occlusion.[9] Dexamethasone intravitreal implant is recommended as an option for macular edema following central retinal vein occlusion (CRVO). It is recommended as an option for macular edema following branch retinal vein occlusion (BRVO) when treatment when treatment with laser photocoagulation has not been beneficial or is not considered suitable because of macular hemorrhage. [9]

O'Doherty, et al.

A 2008 review of the literature for diabetic macular edema treatment reported on a single study of fluocinolone implant in 97 patients with DME randomized to receive either the implant or standard of care with laser treatment or observation.[10] Studies were evaluated on a standardized data extraction form; however a specific quality assessment was not defined and risk of bias for the fluocinolone study was not evaluated. At 3 years, 58% of patients had resolution of DME and associated improvement in visual acuity, compared to 30% of patients in the control group ($p<0.001$). The most common adverse effects included a higher risk of cataract formation and glaucoma in the treatment group compared to control. A total of 5% of patients required removal of the implant to control the glaucoma. Overall, there was little evidence to support the use of the implant and at the time no available studies were available to make conclusions on superiority or noninferiority of fluocinolone acetate implant to other intravitreal injection.

Cochrane Collaboration

A Cochrane review evaluated the effectiveness and safety of intraocular steroids in treatment DME.[11] Three of the total seven trials examined intravitreal steroids implantation (fluocinolone or dexamethasone). The authors concluded that evidence suggests that steroids administered either by intravitreal injection or surgical implantation may improve visual outcomes in eyes with persistent or refractory DME.

Two trials evaluated fluocinolone implant versus standard of care or observation. At 12 months, there was no evidence of effect on three or more lines improvement in visual acuity (RR 2.73, 95% CI 0.63 to 11.93). The other trial demonstrated a marginal statistically significant effect on three or more lines in visual acuity at 36 months (RR 1.93, 95% CI 1.02 to 3.66). Data was insufficient to combine for a meta-analysis and both trials had a high risk of bias. The dexamethasone implant trial included participants with various underlying causes of macular edema. In a subgroup analysis of DME patients, 58% in the dexamethasone group showed a two-line improvement in vision compared to 21% in the observation group (RR 2.75, 95% CI 1.59 to 4.76) at 3 months. This suggests a beneficial effect from dexamethasone and possible evidence of benefit with the use of fluocinolone. There were many methodology limitations in the fluocinolone data, making it difficult to draw strong conclusions on the magnitude of effect.

Author: M. Herink, Pharm.D.

Systemic therapy vs. Implant therapy:

The Multicenter Uveitis Steroid Treatment Trial Research Group
A recent fair quality randomized, partially masked, controlled trial reported 24-month results of an evaluation of fluocinolone acetonide implant compared to systemic therapy with oral corticosteroids and immunosuppressive drugs when indicated (standard of care) for noninfectious intermediate uveitis, posterior, or panuveitis.[12] The Multicenter Uveitis Steroid Treatment (MUST) Trial compared 129 participants in the implant group to 126 participants in the systemic therapy group. Appropriate randomization methods were used. Patients, clinicians, and coordinators were unable to be masked; however visual acuity outcome examiners were masked. Most baseline demographics and characteristics were similar between groups; however eyes with uveitis in the implant group had poorer visual field sensitivity than those in the systemic group.

Both groups experienced improvement of best-corrected visual acuity (BCVA; a measure of visual acuity) during follow-up at all time points. There was no statistically significant difference between the treatment groups in improvement in visual acuity at 24 months, with a mean improvement from baseline of 6.0 letters in the implant group compared to 3.2 letters in the systemic group (estimated treatment effect 2.70, 95% CI -1.16 to 6.68; p=0.16). At 24 months, 21% and 13% of eyes assigned to implant or systemic therapy, respectively, had gained at least 15 letters (p=0.065). Both groups experienced control of active uveitis, however more frequent in the implant group (88% vs. 71%, p=0.001). Authors concluded that both groups were successful in controlling inflammation in the majority of cases, without clear evidence indicating superiority of effectiveness for either group. The implant has the potential to achieve inflammatory control faster and more often and ocular complications of uveitis or treatment were more common in the implant group.

The implant group had a more than 4-fold higher rate of incidence of intraocular pressure (IOP) elevation ≥ 10 mmHg, absolute IOP of ≥30 mmHg, and of needing medical and surgical treatments for elevated IOP. Glaucoma developed in 17% and 4.0% in the implant and systemic groups, respectively (HR=4.2, 95% CI 1.82-9.63; p=0.0008). Those in the implant group also experienced higher cumulative 24-month risk of both cataract (91% vs. 45%, HR 4.12 95% CI 2.2-7.7; p<0.0001) and cataract surgery (80% vs. 31%, HR 3.3 95% CI 2.2-5.0; p<0.0001). Adverse systemic events were infrequent in both groups and there was no significant difference in risk of hospitalizations.

Pavesio, et al.
A previous poor-fair quality 3-year, open label, randomized, phase 2b/3 superiority study compared fluocinolone implant with standard of care in subjects with unilateral or bilateral noninfectious posterior uveitis.[13] The study was conducted from April 2002 through August 2005 at 37 centers across 10 countries. Subjects were randomized to a 0.59-mg fluocinolone implant (n=66) or SOC (n=74) with either systemic prednisolone or equivalent corticosteroid monotherapy or, if deemed necessary, combination therapy with an immunosuppressive agent plus a lower dose of prednisolone or equivalent corticosteroid. Approved immunosuppressants included cyclosporine A, methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, and tacrolimus. Subjects were allocated to receive either an implant or SOC as determined by a centrally administered randomization procedure. It was not possible to mask study treatments; however efforts were made to avoid selection bias. Treatment allocation was masked until the confirmation of inclusion of the subject and some outcome assessments were masked. There was a statistically significant difference between the treatment groups in gender (p=0.02); other baseline characteristics were similar between the two groups.

The primary outcome was time to first recurrence of uveitis, and 2-year results are included in the study. Using uveitis activity as a primary outcome may bias the results against systemic therapy because systemic regimens rely on tapering medications until uveitis activity returns and then increasing the medication to control inflammation.[14] Subjects that received fluocinolone had delayed onset of observed recurrence of uveitis and statistically significant lower rate or percentage of subjects who had at least 1 recurrence compared with SOC (34.8% vs. 64.9%; p<0.01). The mean time to first recurrence was 6.4±7.0 months and 7.1±7.2 months for implanted eyes and the SOC eyes, respectively. There was no statistically significant difference in visual acuity between the two groups, as measured by improvement in at least 3 lines in BCVA (17.2% of implanted eyes vs. 14.3% of SOC; p=0.66). There were no treatment related nonocular adverse events in the fluocinolone group compared to 25.6% of subjects receiving SOC.

Treatment emergent ocular adverse events occurred in 98.5% of implanted eyes versus 79.7% of SOC eyes with a greater number of serious ocular events in implant eyes. Adverse events commonly observed significantly more in eyes with the implant compared to placebo included cataracts requiring extraction (87.8% vs. 19.3%, p<0.01), and increased IOP requiring surgery (21.2% vs. 2.7%, p<0.01). Other serious ocular events included 3 cases of endophthalmitis (4.5%) in the plant group compared to none in the SOC eyes. None of the subjects in the implant group experienced a nonocular adverse event related to treatment, whereas 19 (25.7%) subjects in the SOC group did. The authors concluded that based on the results of the study, the fluocinolone acetonide intravitreal implant seemed to be more effective than SOC therapy in controlling the intraocular inflammation in those with posterior uveitis. It was also associated with increased rates of cataract development and elevated IOP which were managed by surgical or medical treatment.

Diabetic macular edema:

Pearson, et al.

A prospective, fair quality, randomized, 4 year clinical trial studied reported the 3-year efficacy and safety results evaluating fluocinolone implant compared to standard of care in 196 patients with diabetic macular edema (DME).[15] This was evaluator-masked only (patients and investigators were not masked) trial comparing 0.59 mg fluocinolone implant (n=127) to standard of care (n=69) with focal/grid laser photocoagulation or observation at the investigators' discretion. The primary efficacy outcome was ≥15 letter increase in visual acuity at 6 months, measured by masked, certified examiners using a standardized Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Demographic characteristics were similar between the two groups. Improvements in visual acuity were seen in both treatment groups. Though 31.1% of patients reached the primary endpoint, the results were not statistically different from standard of care (p=0.015). At both 6 and 9 months, visual acuity was significantly higher with the implant than with standard of care (p<0.0012 and p<0.002, respectively), but the difference was not significant at 1 year (p=0.119) or 3 years (p=0.1566). There was also a significant difference in change from baseline in macular edema at 6 months and 1 year, but no difference was seen at 3 years (p=0.861).

There was a higher rate of ocular adverse events in eyes treated with the implant than in eyes receiving standard of care (100% vs. 88.4%). The most common adverse effects in implanted eyes were elevated intraocular pressure (69.3%), worsening cataract (55.9%), vitreous hemorrhage (40.2%), and pruritus (38.6%). The most frequent adverse events in SOC eyes were macular edema (36.2%), reduced visual acuity (23.2%), worsening cataract (21.7%), and pruritus (21.7%). Rates of nonocular adverse events were similar in both groups.

Campochiaro et al.

Two identical fair-quality randomized, double blind, sham injection-controlled studies were conducted comparing low (0.2 mcg/day) and high dose (0.5 mcg/day) fluocinolone acetonide intravitreal inserts in 956 patients with DME over a 36-month period. The primary outcome measure was the percentage of

subjects with improvement in baseline BCVA of 15 letters or more at month 24. In the modified intention to treat analysis, both of the fluocinolone insert groups had more subjects showing an improvement in BCVA letter score of 15 or more at 24 month (26.1% in the low-dose group, 26.7% in the high-dose group, 13.0% in the sham group/ $p<0.001$).

The most common serious adverse event was cataract surgery, which occurred in 50.9% of patients in the high-dose implant group, 41.1% in the low-dose group, and 7.0% in the sham group. Increased IOP and glaucoma also occurred more frequently in the implant groups than in the sham group. Overall attrition was 19% in the high-dose group, 19.9% in the low-dose group, and 22.7% in the sham group. Withdrawals due to adverse events were higher in the high-dose group than both the low-dose group and the sham group (5.1%, 1.1%, and 1.6%, respectively). The incidence of serious cardiovascular events was similar in the 3 groups (sham 10.3%, low-dose 12.0%, and high-dose 13.2%). However, myocardial infarction occurred in 4.0% of patients in the low dose implant group compared to 1.1% in the sham group ($p=0.0347$). The authors suggested this is highly likely a result of chance because the release of fluocinolone within the eye is so low that levels are not measurable in the systemic circulation.

Dexamethasone: Haller, et al.

A prospective, poor quality, randomized, single-masked controlled trial evaluated the safety and efficacy of two doses of the dexamethasone implant compared to observation in patients with DME.[16] The primary outcome was the proportion of eyes that achieved an improvement in BCVA of 10 letters or more at day 90. A statistically significant difference in the primary outcome was shown at day 90 (33% vs. 12%, $p=0.07$, 95% CI for difference, 6.14% to 35.96%). The differences between the low and high dose dexamethasone groups (300 mcg and 700 mcg) were not statistically significant. There was no significant difference in the number of cataract between the groups. There was a significant difference in the number of subjects experiencing increased IOP in the dexamethasone groups compared to observation (14.5% vs. 9.4% vs. 0%; $p=0.006$). [16] This was a sub-analysis of a larger study including patients with macular edema from additional causes including retinal vein occlusion, uveitis, and Irvine-Gass syndrome, and therefore should be interpreted with caution.

References:

1. Bausch & Lomb. retisert prescribing information. Available at: http://www.bauschvrx.com/retisert_prescribing_information.pdf. Accessed September 18, 2012.

2. Guly CM, Forrester JV. Investigation and management of uveitis. *BMJ*. 2010;341:c4976.

3. Nguyen QD, Hatef E, Kayen B, et al. A cross-sectional study of the current treatment patterns in noninfectious uveitis among specialists in the United States. *Ophthalmology*. 2011;118(1):184–190.

4. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am. J. Ophthalmol.* 2005;140(3):509–516.

5. Callanan DG, Jaffe GJ, Martin DF, Pearson PA, Comstock TL. Treatment of posterior uveitis with a fluocinolone acetonide implant: three-year clinical trial results. *Arch. Ophthalmol.* 2008;126(9):1191–1201.

6. Lowder C, Belfort R Jr, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch. Ophthalmol.* 2011;129(5):545–553.

7. Stewart MW. Corticosteroid use for diabetic macular edema: old fad or new trend? *Curr. Diab. Rep.* 2012;12(4):364–375.

8. Oregon Pharmacy & Therapeutics Committee. Abbreviated Class Review: Vascular Endothelial Growth Factor Inhibitors. 2012. Available at: http://pharmacy.oregonstate.edu/drug_policy/index.php.

9. National Institute for Health and Clinical Excellence. Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion. *NICE*. 2011. Available at: http://www.nice.org.uk/. Accessed October 31, 2012.

10. O'Doherty M, Dooley I, Hickey-Dwyer M. Interventions for diabetic macular oedema: a systematic review of the literature. *Br J Ophthalmol*. 2008;92(12):1581–1590.

11. Grover D, Chong C. Intravitreal steroids for macular edema in diabetes. *Cochrane Database of Systematic Reviews*. 2008;(1).

12. Kempen JH, Altaweel MM, Holbrook JT, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. *Ophthalmology*. 2011;118(10):1916–1926.

13. Pavesio C, Zierhut M, Bairi K, Comstock TL, Usner DW. Evaluation of an intravitreal fluocinolone acetonide implant versus standard systemic therapy in noninfectious posterior uveitis. *Ophthalmology*. 2010;117(3):567–575, 575.e1.

14. Holbrook JT, Kempen JH, Prusakowski NA, Altaweel MM, Jabs DA. Challenges in the design and implementation of the Multicenter Uveitis Steroid Treatment (MUST) Trial--lessons for comparative effectiveness trials. *Clin Trials*. 2011;8(6):736–743.

15. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology*. 2011;118(8):1580–1587.

16. Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. *Arch. Ophthalmol.* 2010;128(3):289–296.

Author: M. Herink, Pharm.D.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Class Update: Overactive Bladder

Month/Year of Review: January 2013
PDL Class: Genitourinary – Overactive Bladder
New drug: Mirabegron (Myrbetriq™)
End date of literature search: September 2012

Date of Last Review: 2006
Source Document: DERP Report
Manufacturer: Astellas Pharma Technologies, Inc.

Current Status of PDL Class:

- Preferred Agents: Fesotodine Fumarate (Toviaz®), hyoscyamine drops/elixir, hyoscyamine ER tablets, oxybutynin tablets/syrup, oxybutynin patch (Oxytrol®), oxybutynin ER tablets, and tolterodine (Detrol®)
- Non Preferred Agents: Darifenacin (Enablex®), flavoxate (Urispas®), solifenacin (Vesicare®), tolterodine ER (Detrol LA®), trospium (Sanctura®), trospium ER (Sanctura XR®), and oxybutynin Gel packet (Gelnique®)

Research Questions:

- Is there any new relevant evidence from high quality systematic reviews or evidence-based guidelines demonstrating differences in efficacy or safety between anticholinergic drugs, suggesting recommended changes to the current management of the Overactive Bladder (OAB) class?
- Is mirabegron more effective and/or safer than currently available agents?
- Are there subgroups of patients where mirabegron may be more effective or safer than currently available agents?

Conclusions:

- There is no consistent new evidence from available systematic reviews to change the previous conclusions, and no strong evidence to distinguish between agents in efficacy or adverse events.
- There is low quality evidence that comparisons of extended-release and immediate release formulations tended to find higher rates of adverse events, particularly dry mouth, with immediate release formulations, however no differences in discontinuation rates were found.
- There is low-moderate quality of evidence, based on limited published data, that mirabegron improves short term efficacy outcomes including change in mean number of incontinence episodes and micturitions in 24 hours, compared to placebo and is generally well tolerated. Data came from two short term (12 week) published trials (one good quality; one fair quality).
- There is insufficient direct evidence comparing mirabegron to other agents for the treatment of OAB.

Recommendations:

- Due to the lack of long term clinical outcome data and direct comparative data suggesting superior efficacy or tolerability of mirabegron over currently available agents, compare costs of agents in class in executive session and continue to include both ER and IR options as preferred alternatives.

Previous HRC Conclusions:

- There is no available data on flavoxate.
- There is insufficient evidence to distinguish difference in efficacy or adverse events between available agents
- There is no consistent evidence of an advantage for extended release formulations.

Reason for Review:

In 2006, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the overactive bladder drugs. Since this review, in 2009 the Oregon Evidence-based Practice Center (EPC) Drug Effectiveness Review Project (DERP) completed an updated report for the drug class review. In addition, in June 2012, mirabegron was approved by the FDA for the treatment of overactive bladder. It is the first oral overactive bladder treatment with a distinct mechanism of action since the launch of anticholinergics 30 years ago. This update will examine the place in therapy for mirabegron, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Background:

The International Continence Society defines OAB as urinary urgency, with or without urge incontinence, usually with urinary frequency and nocturia, in the absence of pathologic or metabolic factors that would explain these symptoms[2]. Overactive bladder is characterized by the presence of involuntary bladder contractions that occur during bladder filling despite the patient's attempt to suppress them. Bladder contraction is mediated via cholinergic muscarinic receptors in bladder smooth muscle. The most common cause of overactive bladder syndrome is detrusor overactivity. It is a common disabling condition that affects health-related quality of life.[3]

While urge incontinence is not inevitable, its incidence does increase with age. Epidemiological studies of men and women from North America have reported a prevalence of OAB of 16.0% and 16.9%, respectively[4]. In women, prevalence of urge incontinence increased with age from 2.0% to 19% with a marked increase after 44 years of age, and in men, increased with age from 0.3% to 8.9% with a marked increase after 64 years of age. Among all age groups, OAB without urge continence was more common in men than in women.[4]

Before the treatment of overactive bladder syndrome, a clear diagnosis must be made. Anticholinergics are the main pharmacologic treatments for over active bladder. Anticholinergics work as competitive muscarinic receptor antagonists causing the detrusor muscle to relax and thus reduce the frequency and intensity of contractions of the bladder. Anticholinergic agents have been included in a number of reviews of drugs with high risk of adverse effects in the elderly. These medications reduce symptoms but also can commonly have non-life-threatening side effects such as dry mouth, constipation, dry or itchy eyes, blurred vision, dyspepsia, UTI, urinary retention and impaired cognitive function. The new FDA approved drug mirabegron has a novel mechanism of action that works by stimulating the beta 3-adrenergic receptors in the detrusor muscle of the bladder, causing relaxation of the bladder muscle during the storage phase of the micturition (urination) cycle. It is theorized that due to lack of direct anticholinergic effects, common adverse events associated with anticholinergics, such as dry mouth, constipation, will be avoided. Clinically appropriate measures of effectiveness include change in mean number of incontinence episodes or micturitions per 24 hours, subjective patient assessments of symptoms, and quality of life.

Author: B. Liang, Pharm.D.

Methods:
A Medline (Ovid) literature search was conducted since the end of the literature included in the DERP report for new randomized controlled trials (RCT's) and controlled clinical trials comparing medications head-to-head in the treatment of overactive bladder using all included drugs and limits for humans, English language. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Drug Effectiveness Review Project (DERP); 2009[1]
No effectiveness trials were found and the included trials assessed efficacy outcome measures and were short (-12 weeks). Most of the trials were of fair internal validity, but their applicability to community practice was difficult to determine, as the studies generally excluded patients who would have been at risk of serious adverse events from anticholinergic drugs.

Comparative efficacy (Fair quality of evidence)
• When extended-release and immediate-release formulations of the same drug were compared, no differences in efficacy were found.
• Comparisons of different drugs in extended-release and immediate-release formulations more often found the extended-release drug to be superior, but not in all cases.
• No difference among immediate-release products was found.
• For oxybutynin extended-release compared with tolterodine extended-release the better of 2 studies found them equal.

Adverse events
• In longer-term observational studies, poor quality of evidence demonstrated dry mouth was the most common adverse event for all the drugs, with similar rates between drugs. One comparative study found a higher rate and earlier withdrawal with oxybutynin compared to tolterodine, but rates for both drugs were high.
• Short-term trials (fair quality evidence) making direct comparisons indicate a higher incidence of adverse events overall and specifically dry mouth with oxybutynin than with the other drugs. Differences in adverse event profiles between long-acting products and short-acting products are unclear.

Subpopulations
• Evidence from 5 studies was not consistent in identifying differences between men and women in response to tolterodine (poor quality evidence).

Author: B. Liang, Pharm.D.

• Older patients were found to respond to oxybutynin, tolterodine extended-release, darifenacin, or solifenacin in post hoc subgroup analyses. Adverse event profiles were similar to those found in the overall trial populations (fair quality evidence).
• Oxybutynin immediate-release and tolterodine immediate-release resulted response and adverse event rates that were similar for Chinese women and for primarily white populations of other studies. Solifenacin was found to have response and adverse event rates in a Hispanic subgroup that were similar to those of the overall trial population in 1 study. Tolterodine extended-release and tolterodine immediate-release were found to be similarly effective in Japanese and Korean women, with fewer adverse events in the tolterodine extended-release group. The Japanese patients were shown to have improved quality of life in both groups; no such analysis was undertaken for the Korean patients.

Flavoxate, scopolamine, and hyoscyamine
• Head-to-head comparisons with flavoxate were poor quality and there were no head-to-head comparisons of scopolamine, or hyoscyamine to another drug for OAB.

Cochrane Collaboration
In March 2012, a Cochrane Review by Madhuvrata P et al. was conducted to compare and determine the differential effects of anticholinergic drugs in the treatment of overactive bladder[5]. The review included 86 trials that compared different anticholinergic drugs for overactive bladder symptoms. In the studies that compared oxybutynin and tolterodine, no statistically significant difference was demonstrated in quality of life (standardized mean difference [SMD] -0.00, 95%CI -0.18 to 0.18; 3 trials), proportion of people reporting cure or improvement (RR 1.01, 95%CI 0.93 to 1.11; 5 trials), or leakage episodes per 24 hours (weighted mean difference [WMD] 0.08, 95% -0.16 to 0.31; 7 trials). Eight trials reported withdrawals due to adverse events and found fewer withdrawals in patients taking tolterodine compared to oxybutynin (6% vs. 12.5%, RR 0.52,95% 0.40 to 0.66) at 8-12 weeks. Dry mouth was the most frequently reported side effect and those taking tolterodine experienced dry mouth statistically significantly less frequently compared to participants taking oxybutynin (RR 0.65, 95% CI 0.60 to 0.71).

Five studies were included that compared trospium versus oxybutynin. No statistically significant difference between groups on reported cure or improvement was found (RR 1.00, 95%CI 0.90 to 1.11; 2 trials) and fewer withdrawals due to adverse events occurred in the trospium group compared to oxybutynin (RR 0.66, 95%CI 0.48 to 0.91; 3 trials). In the two trials that compared propanthelin IR versus oxybutynin IR, there was a statistically significant difference in proportion of patients reporting cure or improvement in favor of oxybutynin (RR 0.71, 95%CI 0.53 to 0.96), but no significant difference in withdrawals due to adverse events (RR 1.43, 95%CI 0.53 to 3.89).).

Five trials were included that compared solifenacin to tolterodine. A statistically significant better quality of life was demonstrated (SMD -0.12, 95% CI 0.23 to -0.01, 4 trials), a statistically significant better cure or improvement (RR 1.25, 95%CI 1.13 to 1.39; 2 trials) and fewer leakage episodes (WMD -0.30, 95%CI -0.53 to -0.08) with solifenacin compared to tolterodine. However, there was no statistically significant difference between withdrawals due to adverse events (RR 1.27, 95%CI 0.84 to 2.23; 5 trials) or dry mouth (RR 1.04, 95% CI 0.89 to 1.22). Three trials combined showed statistically significant better quality of life with fesoterodine compared to ER tolterodine (SMD -0.20, 95%CI -0.27 to -0.14), higher reported cure or improvement (RR 1.11, 95%CI 1.06 to 1.16) and less symptoms. The analysis showed significantly higher withdrawals due to adverse events (RR 1.45, 95% CI 1.07 to 1.98) and dry mouth (RR 1.80, 95% CI 1.59 to 2.05) with fesoterodine compared to tolterodine..

An analysis was also conducted comparing IR and ER dosage formulations. Extended versus immediate release preparations of oxybutynin or tolterodine, or both demonstrated no statistically significant differences for cure or improvement, leakage episodes or micturitions in 24 hours or withdrawals due to adverse events, but this was based on limited data. Overall, ER preparations had less risk of dry mouth at 2 to 12 weeks. When comparing ER preparations versus another ER preparation, there was less risk of dry mouth with ER tolterodine than oxybutynin (RR 0.75, 95% CI 0.59 to 0.95) but no difference between transdermal oxybutynin and ER oral tolterodine.

The authors concluded when the prescribing choice is between oral immediate release oxybutynin or tolterodine, there is evidence that tolterodine had less risk or dry mouth (RR 0.65, 95% CI 0.60-0.71) but no difference in efficacy outcomes. There is evidence of reduced risk of dry mouth with extended release preparations of oxybutynin or tolterodine compared to immediate release preparations. Between solifenacin and immediate release tolterodine, there were statistically significant differences for quality of life, patient reported cure or improvement, and urgency episodes in 24 hours, all favoring solifenacin. There was low evidence that solifenacin was associated with less risk of dry mouth compared to tolterodine. Between fesoterodine and extended release tolterodine, evidence from three trials demonstrated fesoterodine might be preferred for superior efficacy but has a higher risk of withdrawal due to adverse events and higher risk of dry mouth. There is little or no evidence available about long-term outcomes in these studies. There were insufficient data from trials of other anticholinergic drugs to draw any conclusions. This review conducted both heterogeneity and sensitivity analyses. The authors evaluated for the risk of bias in included studies and found that: 1) allocation sequence was only adequately generated in 19 trials; 2) although 70 trials were double blinded, only 3 trials specifically stated the outcome assessors were blind to group allocation; 3) in 44 trials the evaluation of treatment efficacy was conducted based on intention-to-treat principals. Thirteen trials specifically stated that a per protocol analysis was used to assess treatment efficacy; 4) Thirty of the 86 trials (38%) declared pharmaceutical company support; 6) in the majority of included trials, the primary endpoint was measured after 12 weeks or less of treatment. Due to these limitations, the results of the review should be interpreted with caution. In addition to these potential biases, the short duration of most studies (12 weeks or less) and the lack of long-term follow up gave littler information about the long-term effects and tolerance of the different anticholinergic agents.

Agency for Healthcare Research and Quality (AHRQ)

A systematic review was performed to evaluate the treatment of overactive bladder in women.[6] This review found that the strength of the evidence for the management of OAB with pharmacologic treatment is weak to moderate for short term outcomes and weak for long term outcomes and harms. All treatments were effective at improving one or more OAB symptoms when compared to placebo. Reductions ranged from 0.9 to 4.6 in incontinence episodes per day across all drug treatments and from 0.7 to 4.2 in voids per day. Study by study, extended release formulations achieved modestly better effects than immediate release, statistical significance varied. No one drug was definitively superior to others[6] . As estimated by metaanalysis, extended release forms (taken once a day) reduce urinary urge incontinence by 1.78 (95 percent CI: 1.61, 1.94) episodes per day, and voids by 2.24 (95 percent CI: 2.03, 2.46) per day. Immediate release forms (taken twice or more a day) reduce UUI episodes by 1.46 (95 percent CI: 1.28, 1.64) per day, and voids by 2.17 (95 percent CI: 1.81, 2.54) per day. Of note, placebo reduces UUI episodes by 1.08 (95 percent CI: 0.86, 1.30), and voids by 1.48 (95 percent CI: 1.19, 1.71) per day. [6]

Fourteen RCTs were identified that directly compared pharmacologic agents. In the majority of comparisons, neither drug was reported more effective at reducing either incontinence episodes or voids per day with a few exceptions. Both oxybutynin ER and tolterodine ER demonstrated superiority in reducing urge incontinence episodes over tolterodine IR. Oxybutynin ER was more effective at reducing voids per day than tolterodine in IR or ER forms. [6] Given heterogeneity of participant populations and study designs, this limited number of studies is insufficient for any drug to be considered definitively superior.

Author: B. Liang, Pharm.D.

New Guidelines:

The American Urological Association was recently updated in 2012 for the diagnosis and treatment of overactive bladder in adults, based on a systematic review of the evidence through December 2011.[7] Quality assessment of individual trials was conducted by an evidence based practice center as well as the evidence strength for the body of evidence. A review of the evidence found no strong evidence for differential efficacy across medications. Therefore, the guidelines recommend the choice of medication be made based on patient's history of anti-muscarinic use, adverse event history, patient preferences, comorbidities, use of other medications, and available resources. Analysis did show different adverse event profiles for dry mouth and constipation. The rate of dry mouth for oxybutynin at 61.4% (95% CI: 52.5% to 69.5%) was statistically significantly higher than the 23.7% (95% CI: 20.7% to 26.9%) rate for tolterodine ($p<0.001$). The treatment recommendations are as follow:

First-Line Treatments:

- Clinicians should offer behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first line therapy to all patients with OAB. *Standard (Evidence Strength Grade B)*
- Behavioral therapies may be combined with anti-muscarinic therapies. *Recommendation (Evidence Strength Grade C)*

Second-Line Treatments:

- Clinicians should offer oral anti-muscarinics including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium (listed in alphabetical order; no hierarchy is implied) as second-line therapy. *Standard (Evidence Strength Grade B)*
- If an immediate release (IR) and an extended release (ER) formulation are available, then ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. *Standard (Evidence Strength Grade B)*
- Transdermal (TDS) oxybutynin (patch or gel) may be offered. *Recommendation (Evidence Strength Grade C)*
- If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti-muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried. *Clinical Principle*
- Clinicians should not use anti-muscarinics in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should use anti-muscarinics with extreme caution in patients with impaired gastric emptying or a history of urinary retention. *Clinical Principle*
- Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. *Clinical Principle*
- Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. *Expert Opinion*
- Clinicians should use caution in prescribing anti-muscarinics in the frail OAB patient. *Clinical Principle*
- Patients who are refractory to behavioral and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. *Expert Opinion*

New Safety Alerts, Indications:

Darifenacin (Enablex) ER has had recent FDA label changes in January and March of 2012. These changes include additions to the adverse reaction in term of anaphylactic reactions, erythema multiforme and interstitial granuloma annulare as well as additions to warnings and precautions about the associated with anticholinergic central nervous system effects.[8]

Author: B. Liang, Pharm.D.

In June of 2012, solifenacin succinate (Vesicare) was also noted to have central nervous system effects. The CNS anticholinergic effects that have been reported include headache, confusion, hallucinations and somonolence.[9]

In March 2012, the FDA changed the safety labeling of oxybutynin by adding glaucoma as an adverse reaction. Angioedema was added onto the warning section of oral oxybutynin's label in December of 2010.[10]

Fesoterodine (Toviaz) also received a warning for angioedema in February 2011. Later that year, in December, pruritis and urticaria were added under adverse reactions in the updated label of fesoterodine ER 4 mg tablets.[11]

New Drug Evaluation:

FDA approved indications:

Mirabegron (Myrbetriq™) was FDA approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Potential Off-label Use:

Mirabegron has evidence available for use in males with lower urinary tract symptoms and bladder outlet obstruction, on intraocular pressure in normotensive patients, and cardiac repolarization.[12]

Clinical Efficacy Data:

Approval and primary evidence for the efficacy of mirabegron was based on three randomized, double blind, phase III, placebo controlled, 12 week trials.[6]. The population of these studies included treatment naïve patients and patients who had been previously treated with OAB antimuscarinic therapy. All studies included a 2 week single-blind placebo run-in period followed by a 12-week double blind treatment period. The co-primary efficacy endpoints were change from baseline to final visit in mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. The secondary endpoints included change from baseline to final visit in mean volume voided per micturition, and change from baseline to week 4 in mean number of incontinence episodes and number of micturition per 24 hours[6]. Currently, only one of these studies has been published (Study 046) and is included in the evidence table below. The other two efficacy and safety trials have not been published, and therefore a critical appraisal was not performed. Study 046 also included an active control group (tolterodine SR 4 mg daily) to allow comparison to effect size, although this was not a comparative superiority trial.

Study 046 was a randomized, double-blind, placebo and active-control trial comparing the efficacy and safety of mirabegron 50mg (n=497), 100mg (n=498), and tolterodine 4mg SR (495) to placebo (n=497) after 12 weeks of treatment in 27 countries in Europe and Australia. No comparisons were made between mirabegron and tolterodine. The primary endpoints showed 1) A statistically significant difference in mean number of incontinence episodes per 24 hrs between placebo and treatment groups: mirabegron 50mg vs. placebo: -0.41 (p=0.003,CI -0.72,-0.09); mirabegron 100mg vs. placebo: -0.29 (p=0.010,CI -0.61,0.03); and tolteradine 4mg vs. placebo: -0.10 (p=0.11,CI -0.42,0.21); 2) Difference in mean number of micturition episodes per 24 hrs between placebo and treatment groups: mirabegron 50mg vs. placebo: -0.60 (p<0.001,CI -0.90,-.029); mirabegron 100mg vs. placebo: -0.44 (p=0.005,CI -0.74,-0.13); and tolteradine 4mg vs. placebo: -0.25 (p=0.11,CI -0.55,0.06).

Clinical Safety:[6]
The safety of mirabegron was investigated in 1462 individuals in the phase 1 studies and 5863 patients in phase 2/3 studies, of which 622 patients with OAB received for at least 1 year. Serious adverse events, adverse events, and adverse events leading to permanent discontinuation of study drug were reported by 1.7%, 53.4% and 3.6% for mirabegron, 1.8%, 55.2%, and 2.9% for placebo, and 1.7%, 60.2% and 3.8% for tolterodine patients, respectively. There was no apparent dose response across mirabegron groups. Antimuscarinic side effects, specifically dry mouth, were reported less frequently in mirabegron-treated patients (2%) compared with tolterodine-treated patients (11.1%) in the 12 week trials and 2.6% versus 8.6% in the long-term study. Dry mouth was reported with a similar frequency in mirabegron-treated and placebo-treated patients in the 12 week studies. In these same studies, tachycardia and palpitations were reported as an AE in the mirabegron 50 mg group (1.2%; 0.4%) at a higher frequency than placebo (0.6%; 0.1%).

Mirabegron administered at 50 mg once daily was associated with an increase in pulse rate of approximately 1 beat per minute (bpm) compared with placebo in patients with OAB. In the phase 3 studies, a low proportion of mirabegron 50 mg-treated patients reported any occurrence of tachycardia (57/1375, 4.1%) at a frequency greater than placebo-treated patients (48/1380, 3.5%) and tolterodine-treated patients (16/495, 3.2%).

Mirabegron administered at the dose of 50 mg once daily was associated with a mean 0.4 to 0.6 mm Hg change from baseline systolic blood pressure/diastolic blood pressure (SBP/DBP) compared with placebo. Although there was no evidence of an increase in cardiovascular outcomes of death, serious adverse events, ventricular arrhythmias or major adverse cardiac events associated with mirabegron treatment compared to either placebo or tolterodine, due to the nature of short term studies, these result should be interpreted in caution.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:
1) Change in mean number of micturitions per 24 hrs
2) Change in mean number of incontinence episodes per 24 hrs
3) Quality of Life
4) Withdrawals due to adverse effects

Primary Study Endpoint:
1) Change from baseline in mean number of incontinence episodes
2) Micturitions per 24 hours

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Duration	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Study 046 Phase III, randomized double-blind, placebo-controlled trial	1. Mirabegron 50 mg daily 2. Mirabegron 100 mg daily 3. Tolterodine ER 4 mg daily 4. Placebo 12-week treatment duration	Demographics: Inclusion Criteria: OAB for at least 3 months, on average >8 micturitions per 24 hours, at least 3 episodes of urgency (grade 3/4) with or without incontinence in 3-day diary period, treatment naïve or prior anitmuscarinic therapy Exclusion Criteria:	ITT:1978 PP: Attrition:	2-week single-blind placebo run-in followed by 12-month double-blind treatment period	<u>Difference in mean number of incontinence episodes per 24 hrs:</u> M50 v P: -0.41 (p=0.003,CI -0.72,-0.09) M100 v P: -0.29 (p=0.010,CI -0.61,0.03) T4 v P: -0.10 (p=0.11,CI -0.42,0.21) <u>Difference in mean number of micturition episodes per 24 hrs:</u> M50 v P: -0.60 (p<0.001,CI -0.90,-.029) M100 v P: -0.44 (p=0.005,CI -0.74,-0.13) T4 v P: -0.25 (p=0.11,CI -0.55,0.06) Percentage of responders (patients with a 50% or greater decrease from baseline in the mean number of incontinence episodes per 24 h) M50: 72% M100: 67.6% Tolt: Pla: 60.1% M50 vs. Pla: OR 1.75, 95% CI 1.23-2.49; p=0.002 M100 vs. Pla: OR 1.45, 95% CI 1.02-2.05 P=0.037	N/A N/A	<u>Discontinuations due to adverse events:</u> M50: 25 (5%) M100: 16 (3.2% Tolt: 24 (4.8%) Pla: 13 (2.6%)	NS	**Quality Rating:** Good **Internal Validity: RoB** <u>Selection:</u> Randomization done using a computer-generated randomization scheme; allocation to groups was accomplished using an interactive response system. Similar baseline characteristics <u>Performance:</u> Patients were blinded t the identity of the study drug and investigators were blinded to identity of assigned drug. <u>Detection:</u> No information included i outcome assessors were blinded. <u>Attrition:</u> Total attrition approximately 10% and similar rates between groups. Efficacy was assessed using the full analysis set, which included all randomized patients who took at least one dose of the study drug and had at least a baseline and one post baseline micturition measurement, which included 96% of total randomized patients. **External Validity:** <u>Recruitment:</u> 27 countries in Europe and Australia <u>Patient Characteristics:</u> Approximately half of the patients had received previous treatment with OAB medication. <u>Outcomes:</u> Short-term only; not true effectiveness outcomes.

References:

1. McDonagh MS, Selover D, Santa J, Thakurta S. Drug Class Review: Agents for Overactive Bladder. Update 4. Available at: http://derp.ohsu.edu/about/final-products.cfm. Accessed July 11, 2012.

2. Bernard Haylen D de R. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *International urogynecology journal and pelvic floor dysfunction*. 2009.

3. Abrams P, Kelleher CJ, Kerr LA, Rogers RG. Overactive bladder significantly affects quality of life. *Am J Manag Care*. 2000;6(11 Suppl):S580–590.

4. Stewart, Van Rooyen, Cundiff, et al. Prevalence and burden of overactive bladder in the United States. *World Journal of Urology*. 2003;20(6):327–336.

5. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJC. Which anticholinergic drug for overactive bladder symptoms in adults. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005429.pub2/abstract. Accessed July 10, 2012.

6. Hartmann K, McPheeters M, Biller D, et al. Treatment of Overactive Bladder in Women. Evidence Report/Technology Assessment No. 187 (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). AHRQ Publication No. 09-E017. Rockville, MD: Agency for Healthcare Research and Quality. August 2009.

7. Gormley EA, Lightner DJ, Burgio K, et al. OAB_guideline.pdf. 2012. Available at: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/ic-bps/diagnosis_and_treatment_ic-bps.pdf. Accessed July 10, 2012.

8. Commissioner O of the. Safety Information - Enablex (darifenacin) extended-release tablets. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm233702.htm. Accessed July 11, 2012.

9. Commissioner O of the. Safety Information - Vesicare (solifenacin succinate) tablet. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm227976.htm. Accessed July 11, 2012.

10. Commissioner O of the. Safety Information - Ditropan (oxybutynin chloride) tablets. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm175916.htm. Accessed July 11, 2012.

11. Commissioner O of the. Safety Information - Toviaz (fesoterodine fumarate) extended release tablets. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm245803.htm. Accessed July 11, 2012.

12. Myrbetriq (mirabegron). AMCP Dossier. Astellas Scientific and Medical Affairs, Inc. Northbrook, IL 60062.

Author: B. Liang, Pharm.D.

Appendix 1: Specific Drug Information[13]

CLINICAL PHARMACOLOGY

Mirabegron is a beta-3 adrenergic receptor agonist. It relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 adrenergic receptor which increases bladder capacity. Stimulation of the beta-1 adrenergic receptor occurs at a mirabegron dose of 200mg.

PHARMACOKINETICS

The absorption and elimination pharmacokinetics of mirabegron are dose-dependent.

Parameter	Result
Oral Bioavailability	Dose dependent: 29% (25mg dose) and 35% (50mg dose)
Protein Binding	71% (albumin and alpha-1 acid glycoprotein)
Elimination	55% in urine and 34% in feces
Half-Life	50 hours
Metabolism	CYP3A4, CYP2D6, UGT, butylcholinesterase

DOSE & AVAILABILITY

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
ER 25mg ER 50mg	Tab	PO	Daily	The daily dose should not exceed 25 mg in patients with severe renal impairment (CLcr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73m2); Not recommended in end stage renal disease	The daily dose should not exceed 25 mg in patients with moderate hepatic impairment (Child-Pugh Class B); Not recommended in severe hepatic impairment	The safety and effectiveness in pediatric patients have not been established	No dose adjustment is necessary for the elderly.	With or without food. Recommended starting dose is 25 mg once daily, which is effective within 8 weeks. The observed Cmax and AUC were approximately 40-50% higher in females compared to males. However, when normalized by body weight, it reduces to about 20-30%

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no Serious Drug Safety concerns or contradictions for mirabegron at this time.

Warnings and Precautions:

Author: B. Liang, Pharm.D.

Mirabegron can increase blood pressure therefore periodic blood pressure readings are recommended, especially in hypertensive patients. It is not recommended for use in patients with severe uncontrolled hypertension, which is defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mmHg. Two recent studies found mirabegron associated with dose-related increases in supine blood pressure in healthy individuals. The maximum recommended dose of 50 mg was found to have a mean maximum increase in systolic/diastolic blood pressure of approximately 3.5/1.5 mmHg greater than placebo. In trials with OAB patients, the mean increase in systolic and diastolic blood pressure at the maximum recommended dose was approximately 0.5 to 1 mmHg greater than placebo. Worsening of pre-existing hypertension was reported infrequently in mirabegron patients.

Mirabegron may increase the chance of urinary retention in patients with bladder outlet obstruction (BOO) or patients taking antimuscarinic medications for the treatment of OAB. Clinical studies in patients with BOO did not demonstrate increased urinary retention in mirabegron patients, but mirabegron should still be administered with caution to patients with clinically significant Boo and in patients taking antimuscarinic medications for the treatment of OAB.

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates (e.g. metoprolol and desipramine) is increased when co-administered with mirabegron. Approriate monitoring and dose adjustment may be necessary, especially with drugs that are metabolized by CYP2D6 (e.g. thioridazine, flecainide, propafenone).

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
No look-alike/sound-alike drugs have been found to have error risk potential.

Adverse Reactions

Hypertension was the most common adverse reaction among the placebo and mirabegron study groups. The 50mg dose of mirabegron caused a similar amount of hypertension incidences to placebo whereas the 25mg mirabegron group had a higher incidence of hypertension in comparison to placebo.

	Placebo (%)	**Mirabegron 25mg (%)**	**Mirabegron 50mg (%)**
Number of Patients	**1380**	**432**	**1375**
Hypertension	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory Tract Infection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

New Drug Evaluation: Aclidinium bromide

Month/Year of Review: January 2013
Generic Name: Aclidinium bromide
PDL Class: Pulmonary- anticholinergic inhalers

End date of literature search: November 2012
Brand Name (Manufacturer): Tudorza Pressair® (Forest Pharmaceuticals)
Dossier Received: Pending

FDA Approved Indication: Aclidinium bromide is an anticholinergic indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including bronchitis and emphysema.

Research Questions:
- Is aclidinium safe and effective in the maintenance treatment of bronchospasm associated with COPD?
- How does the efficacy and safety of aclidinium compare to currently available treatment options?
- Are there subpopulations where aclidinium is more efficacious or safer than other available agents?

35

Conclusions:
- There is moderate quality evidence that twice daily aclidinium is effective at improving lung function in patients with moderate to severe COPD, as measured by the trough FEV_1 after 12 and 24 weeks of treatment, compared to placebo. Trials have been short-term, and the long-term efficacy and safety of aclidinium bromide are not known.
- Published trials use the surrogate marker of change in FEV_1 to evaluate the efficacy of aclidinium, while mortality remains most desired clinical outcome. There remains insufficient evidence to determine its effects on mortality and other patient-orientated outcomes, including exacerbations.
- There are no head-to-head, phase 3 trials comparing aclidinium to tiotropium, which has more long-term data available and is dosed once daily.
- Aclidinium has an acceptable safety profile, which is similar to that of placebo. Serious adverse event rates were low, however the cardiovascular risks of aclidinium are not well defined and need to be studied in larger clinical trials.

Recommendations:
- As an additional long-acting inhaled anicholinergic, aclidinium bromide can be used as an alternative to tiotropium in the maintenance treatment of COPD.
- Due to no evidence demonstrating clinical superiority of this agent over tiotropium and a lack of long-term efficacy and safety data, recommend making aclidinium non-preferred on the PDL.
- Aclidinium should not be used to treat COPD exacerbations until there are studies available that show benefit for this indication.

Background:

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death worldwide with over 60% of the cases worldwide going undiagnosed.[1 2] COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs.[3] The lung parenchyma becomes damaged, causing loss of elastic recoil, which leads to emphysema, and allows for the infiltration of inflammatory cells. The most common risk factor of COPD is tobacco smoking.[1] Other risk factors include indoor air pollution and occupational dusts and chemicals, outdoor air pollution, and factors that affect lung growth during gestation and childhood. There is a genetic component to COPD linked to a deficiency in the protease inhibitor alpha 1-Antitrypsin (A1AT), which protects tissues from enzymes of inflammatory cells.[3] COPD has a higher prevalence among men and prevalence increases with age.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines provide recommendations for the diagnosis, management, and prevention of COPD. Patients are classified as mild, moderate, severe, or very severe based on the forced expiratory volume over one second (FEV_1) divided by the forced vital capacity (FVC). The diagnosis of COPD is done using spirometry and is defined as a $FEV_1/FVC < 0.70$ based on a post-bronchodilator FEV_1.[3]

Therapies for COPD include both non-pharmacologic and pharmacologic options. Smoking cessation remains one of the most important interventions. Other non-pharmacologic options are modification of occupational exposure, reducing or avoiding indoor air pollution, and participating in physical activity. Pharmacologic therapies can be an effective method to reduce the frequency and severity of COPD exacerbations. Optimal therapy must factor in the severity of disease, comorbidities, frequency and severity of exacerbations, cost, and general health status.[3] Classes of medications used to treat COPD are beta2-agonists, anticholinergics, inhaled corticosteroids, methylxanthines, systemic steroids, phosphodiesterase-4 inhibitors, vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic agents, antitussives, and vasodilators. Those with severe COPD have the option of lung volume reduction surgery, which has shown a mortality benefit, and improvement of quality of life.

Patients with COPD have an elevated cholinergic tone which can be partially reversed with anticholinergic agents. Based on the GOLD guidelines, long-acting anticholinergics are the first or second line treatment for patients with mild or moderate COPD and are a part of the first line treatment for patients classified with severe or very severe disease.[3] Ipratropium and tiotropium are two anticholinergic agents that are used to treat COPD; tiotropium is the only long-acting anticholinergic previously available.[3] Guidelines from the National Institute for Health and Clinical Excellence (NICE) National Clinical Guideline Centre also recommend either long-acting beta2 agonist (LABA) or long acting anticholinergic in people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required.

Aclidinium is a new long-acting anticholinergic drug that is administered twice daily. After inhalation, aclidinium selectively inhibits the muscarinic M3 receptor, which in turn causes bronchodilation. Because of its selectivity, patients using aclidinium could potentially be at lower risk for anticholinergic side effects that are a result of nonselective inhibition of muscarinic receptors.[4] Typical anticholingeric side effects include dry mouth, constipation, and urinary retention. Cardiovascular side effects are also a concern, as anticholinergic agents are associated with an increased risk for stroke, cardiovascular death, and myocardial infarction.

Aclidinium is delivered using the dry powder inhaler, Genuair, which contains 60 doses and contains a dose indicator to alert the user of how many doses remain.[4] After pressing and releasing a green button, 13mg of powder containing 400μg of aclidinium bromide and lactose carrier, is released into a chamber in

Author: Brandy Fouts, Pharm.D.

the inhaler. The control window changes from red to green and the patient should then breathe in quickly and deeply through a mouthpiece. A successful inhalation is confirmed by an audible "click".

Clinical Efficacy:

Summary

Two phase 2, double-blind, double-dummy, cross-over trials with active comparators were completed. In the phase 2a trial, patients received aclidinium 400μg, tiotropium 8μg or placebo for 15 days, with a washout between treatment periods. For the primary endpoint of mean change in FEV_1AUC (area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged), aclidinium and tiotropium were significantly better than placebo; treatment differences vs. placebo were 221mL and 244mL, respectively ($p<0.0001$ for both). In the phase 2b trial, patients were randomized to receive twice daily doses of aclidinium 100μg, 200μg, 400μg, formoterol 12μg or matched placebo for 7 days. For the primary endpoint of mean change from baseline in FEV_1 normalized AUC, aclidinium 400μg and formoterol were significantly better than placebo; treatment differences were 208mL and 210mL, respectively ($p<0.0001$ for both). Because of the short durations and small sample sizes (n=30 and 79), these studies will not be further evaluated.

The ACCLAIM/COPD I and ACCLAIM/COPD II studies were phase 3 studies completed that evaluated the efficacy of aclidinium. These studies used a lower dose of aclidinium than what was ultimately approved (200μg once daily was studied, 400μg twice daily was ultimately approved). In these studies, patients treated with aclidinium experienced a statistically significant improvement in lung function, although the clinical significance of the improvement in forced expiratory volume (FEV_1) was called into question by the FDA. These clinical studies with the 200 μg once daily dose will not be evaluated further because this dose is lower than the 400μg twice daily dose recommended, as well as the lack of clinically meaningful efficacy demonstrated. Two additional phase 3 studies were conducted, the ATTAIN and ACCORD COPD I studies, which evaluated the efficacy and safety of twice-daily aclidinium 200μg and 400μg versus placebo. Both studies found that treatment of moderate-to-severe COPD patients with twice-daily aclidinium of either dose was associated with significant improvements in bronchodilation, health status, and COPD symptoms. The treatment effect for the 400μg dose ranged from 61mL to 124mL across the studies at week 12.[5] A minimum clinically important difference for FEV1 has not been defined in COPD, although improvement of around 100 to 140ml has been suggested as a benchmark. Tiotropium has been shown to increase FEV1 by around 140ml compared to placebo. ACCORD COPD II is a third phase III trial evaluating efficacy and safety, however it has not been published yet and therefore cannot be appraised for quality and validity.

The ATTAIN Study

The ATTAIN study is a phase 3 study that evaluates the efficacy and safety of aclidinium bromide in 828 patients from Europe and South Africa with moderate to severe COPD. In the double-blind, placebo-controlled, multicenter, 24 week trial, patients were randomized 1:1:1 to receive aclidinium 200μg twice daily, 400μg twice daily, or placebo. All doses were administered using the multi-dose Genuair dry powder inhaler. The primary endpoint of the study was change in trough FEV_1 at week 24. Efficacy analyses were performed on the intent-to-treat (ITT) population and missing data were imputed using last observation carried forward (LOCF). Results demonstrated that the aclidinium groups showed significant improvements from baseline for FEV_1 for both the aclidinium 200μg and 400μg groups versus placebo (99 and 128 mL; both $p<0.0001$). Both treatment groups showed an improvement in peak FEV_1 from baseline (185 mL for 200μg and 209 mL for 400μg; both $p<0.001$).[7]

Author: Brandy Fouts, Pharm.D.

Quality of life and dyspnea were measured as secondary outcomes, using the St. George's Respiratory Questionnaire (SGRQ) and the Transitional Dyspnea Index (TDI) focal score. The SGRQ is a self-administered health related quality of life measure. A clinically relevant improvement in the SGRQ is defined as ≥4 points on totals score. The aclidinium clinical development program proposed a 1-unit increase as the threshold for meaningful clinical difference in TDI, however there is no regulatory precedent for this and it has not been accepted as a validated measure of dyspnea. Significant improvements were seen in the aclidinium 200μg and 400μg groups over placebo for the baseline-adjusted mean SGRQ total score (-3.8 and -4.6 units; $p<0.001$ for both) and TDI focal score (0.6 and 1.0 nits; $p<0.05$ and $p<0.001$) at week 24.[7] More patients had a clinically significant improvement in SGRQ total score at week 24 with aclidinium 200μg and 400μg compared to placebo (56% vs. 57.3% vs. 41%; OR 1.83 and 1.87, $p<0.001$ for both).

There were fewer COPD exacerbations in the treatment groups compared to placebo (15.9% 200μg, 14.1% 400μg, 20.5% placebo; p value not provided). The rate ratio was statistically significant for exacerbations of any severity for both 200μg (RR 0.72, 95% CI 0.52-0.99; $p<0.05$) and 400μg (RR 0.67, 95% CI 0.48-0.94; $p<0.05$) compared to placebo, however the difference in frequency of moderate or severe exacerbations did not reach statistical significance. Potential anticholinergic adverse events occurred with an incidence of <1% in any treatment group except for urinary tract infections, which showed a higher incidence in the higher dose treatment group (0.7% 200μg, 2.2% 400μg, 0.7% placebo).[7]

The results of the ATTAIN study show that aclidinium improves lung function in patients with moderate to severe COPD. This study showed improvements of both studied aclidinium doses over placebo for the primary endpoint change in trough FEV_1 as well as the secondary endpoints peak FEV_1, heath status (SGRQ) and dyspnea (TDI). The safety profile of aclidinium was similar to placebo. The 400μg dose performed numerically better throughout the study, but the study was not designed to find differences between doses.

ACCORD COPD I Study

The ACCORD COPD I study is a phase 3 study that evaluated the efficacy and safety of twice-daily aclidinium in 561 patients with moderate to severe COPD. In the double-blind, placebo-controlled, multicenter, 12 week trial, patients were randomized 1:1:1 to receive aclidinium 200μg twice daily, aclidinium 400μg twice daily, or placebo. The Genuair multi-dose inhaler was used to administer all doses. The primary endpoint of the study was change from baseline to week 12 in morning predose (trough) FEV_1, the average of 2 predose FEV_1 values. ACCORD COPD I found an improvement in mean trough FEV_1 compared to placebo by 86 (95% CI 45,127) mL in the aclidinium 200μg group and 124 (83,164) mL in the aclidinium 400μg group ($p\leq0.0001$ for both). Similar improvements were seen for improvement in peak FEV_1 from baseline [146 (101,190) mL for the 200μg and 192 (148, 236) mL for the 400μg group; $p\leq0.0001$ for both).[8]

Heath status and COPD symptoms were measured using the SGRQ and TDI respectively. Significant improvements were seen in the SGRQ for patients in the treatment groups compared to placebo at 12 weeks [-2.7 (aclidinium 200μg, $p=0.013$) and -2.5 (aclidinium 400μg, $p=0.019$)]. For TDI focal scores the difference from placebo was significant in the 200μg group of (0.9, p=005) and 400μg group (1.0, $p<0.005$).[8] A trend towards a reduction in the rate of moderate-to-severe COPD exacerbations per patient/year were observed with both doses compared with placebo, however these changes were not significant ($p=0.130$ and $p=0.091$, respectively).

The ACCORD COPD I study showed that aclidinium improves lung function in patients with moderate to severe COPD. Improvements were seen in peak and trough FEV_1 as well as the SGRQ and TDI scores compared to placebo. Improvements were evident the first day of treatment and were maintained during the 12-

week study. The safety profile of both doses of active drug were similar to placebo. The aclidinium 400μg group performed numerically better throughout the study.

Clinical Safety:

Adverse events were mild and similar to placebo across the phase 3 studies. There were a total of four deaths reported in the ATTAIN and ACCORD COPD I studies, three in the patients treated with aclidinium and one in patients using placebo. The causes of death were one from metastatic lung cancer in the ACCORD COPD I study.[8] In the ATTAIN study one subject died from myocardial infarction (200μg), one from acute cardiac failure (400μg), and one from a road traffic accident (placebo).[7] None of the deaths were attributed to the study drug.

Treatment groups of both doses were well tolerated during the studies. In the ACCORD COPD I study, the percentage of patients having a treatment-emergent adverse event was 44.7% in the aclidinium 400μg group, 50.5% in the aclidinium 200μg group, and 52.5% in the placebo group. Fewer COPD exacerbations were reported in the aclidinium 400μg group compared to the 200μg and placebo groups. Incidences of anticholinergic-related adverse effects were <2% in all groups. The incidence of serious adverse effects was 2.2% for placebo, 4.3% aclidinium 200μg, and 3.2% 400μg.[7]

Serious adverse events and discontinuation due to adverse events in the aclidinium studies are not concerning. The overall incidence rate was greater in the placebo group (105 events/1000 patient years) compared to 76 events/1000 patient years) in the aclidinium 400μg group. There was a wide range of events reported and most occurred in one or two patients.[5]

To assess the impact on cardiovascular health, the FDA conducted an analysis of major adverse cardiac events (MACE). The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. The results do not indicate an increased overall MACE score for aclidinium, although the assessment is limited by a relatively small sample size and a low event rate. Some of the differences seen in the studies were due to only one event, which is not enough to make a definitive conclusion. The FDA is requiring Forest Laboratories to conduct a post-marketing study of a larger sample size to address this issue.[5]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of exacerbations
3) Health related quality of life
4) Dyspnea

Primary Study Endpoint:

1) Change from baseline in trough FEV_1 at weeks 12, 24, or 28 weeks
2) Peak FEV_1 at week 12

Author: Brandy Fouts, Pharm.D.

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
RCT, DB, PC, MC ATTAIN Trial 24 weeks	1. Aclidinium 200µg twice daily (200µg) 2. Aclidinium 400µg twice daily (400µg) 3. Placebo twice daily (pbo) All were administered using the Genuair inhaler Concomitant meds permitted: • inhaled corticosteroids • oral sustained-release theophyllines • systemic corticosteroids at doses equivalent to 10mg per day of prednisone or 20mg every other day • oxygen therapy (<15 h per day) • salbumatol prn (had to be discontinued 6 hours prior to and during a study visit)	Demographics (200µg, 400µg,pbo): • Age: 62.3, 62.9, 62.0 yrs • Male: 65, 68, 69% • Current Smoker: 50.5, 55.0, 52.8% • Post-bronchodilator FEV_1: 57.6, 56.2, 56.6 % predicted Inclusion Criteria: • ≥ 40 years old • Diagnosis of COPD per GOLD criteria • Post-bronchodilator $FEV_1/FVC < 70\%$ • FEV_1 <80% • ≥ 10 pack years • Good technique during lung function assessments Exclusion Criteria: • Asthma • Unstable cardiac conditions, including myocardial infarction, within the previous 6 months • Respiratory tract infection or COPD exacerbation 6 wks prior • Contraindication to anticholinergic drugs	Randomized: 200µg – 277 400µg - 269 Pbo - 273	Improvement from baseline of trough FEV_1 at 24 weeks (mean +/- SE) mL: 200µg: 99 ±22 400µg: 128 ±22 p-value: <0.0001 for both Mean peak FEV_1 from baseline with treatment versus placebo at 24 weeks: 200µg vs pbo: 185 ±23 mL 400µg vs pbo: 209 ±24 mL p-value: <0.0001 for both Improvement over placebo in baseline-adjusted mean SGRQ total score (units): 200µg vs Pbo: -3.8 400µg vs Pbo: -4.6 p-value: <0.001 for both Improvement over placebo in baseline-adjusted mean +SE TDI focal score at wee 24 (units): 200µg: 0.6 ±0.3 mL p<0.05 400µg vs Pbo: 1.0 ±0.3 mL p-value: <0.001	NA NA NA NA	Total AEs: 200µg: 54.5% 400µg: 53.5% Pbo: 57.1% p-value: Not reported SAEs: 200µg: 4.3% 400µg: 5.6% Pbo: 5.5% p-value: Not reported Deaths: 200µg: 0.4% 400µg: 0.4% Pbo: 0.4% p-value: Not reported	NA NA NA	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Patients were screened during a 2 week run-in period to assess disease stability and then randomized 1:1:1 afterwards, baseline characteristics simila in all groups. Unclear on randomization technique or on adequate concealment of allocation. Performance: All three groups received doses via multiple-dose dry powder inhaler Detection: Study described as double-blind but no details given; BDI and TDI tests were administered by independent reviewers. Attrition: 14.9% placebo, 8.6% 200µg, 6.3% 400µg **External Validity:** Recruitment: Not reported. Study was conducted in 9 European countries and South Africa. Patient Characteristics: Subjects were about 62 years old with at least 65% being males in each group. Patients had t have at least 10 pack-yrs of smoking and a diagnosis of COPD and had to have goo technique during lung function assessment. Patients were allowed to be on theophyllines, systemic corticosteroids and oxygen therapy (<15 h per day). Setting: Patients had to be stable for ≥4 weeks before screening Outcomes: Limited evidence for patient-orientated outcomes, data in patients with less severe disease, and data comparing aclidinium to tiotropium or long acting beta2 agonists.

RCT, DB, PC, MC ACCORD COPD I Trial 12 weeks	1. 200µg twice daily aclidinium (200µg) 2. 400µg twice daily aclidinium (400µg) 3. Placebo (Pbo) All were administered using the Genuair inhaler	Demographics (200µg, 400µg,Pbo): • Age: 63.1, 64.9, 65.1 yrs • Male: 55, 53, 52% • Current Smoker: 45.7, 42.1, 46.8% • Post-bronchodilator FEV_1: 52.8, 54.1, 54.6 % predicted Inclusion Criteria: • ≥ 40 years old • Post-bronchodilator FEV_1/FVC ≤ 70% • FEV_1 ≥30% but <80% of predicted • ≥ 10 pack years Exclusion Criteria: • Other significant respiratory conditions (including asthma) • Significant cardiovascular conditions, including myocardial infarction within the previous 6 months • Respiratory tract infection or COPD exacerbation ≤6 wks prior (≤3 months if it resulted in hospitalization) • QTc >470 msec • Medical conditions wherein anticholinergic drugs are contraindicated	Randomized: 200µg – 185 400µg - 190 Pbo -186 ITT: 200µg – 152 400µg - 166 Pbo -149 Attrition: 200µg – 17.8% 400µg – 12.6% Pbo -19.9%	Improvement from baseline of trough mean FEV_1 over placebo at 12 weeks (95% CI) mL: 200µg: 86 (45,127) 400µg: 124 (83,164) p-value: <0.0001 for both Change from baseline in peak FEV_1 over placebo at 12 weeks: 200µg: 146 (101,190) mL 400µg: 192 (148,236) p-value: <0.0001 for both Improvements over placebo in baseline-adjusted mean SGRQ total score (units) at 12 weeks: 200µg vs Pbo: -3.2 400µg vs Pbo: -3.6 p-value: <0.001 for both Improvement over placebo in baseline-adjusted mean +SE TDI focal score at week 12 (units): 200µg: 0.9 400µg vs Pbo: 1.0 p-value: <0.005 for both	NA NA NA NA	Treatment-emergent adverse effects: 200µg: 50.5% 400µg: 44.7% Pbo: 52.2% p-value: Not reported SAEs: 200µg: 4.3% 400µg: 3.2% Pbo: 2.2% p-value: Not reported Deaths: 200µg: 0 400µg: 1 patient (patient died 23 days after first drug intake and he had metastatic lung cancer – death found to be unlikely due to drug0 Pbo: 0 p-value: Not reported		**Quality Rating: Fair** **Internal Validity: RoB** Selection: Patients were randomized but not described how and no information on allocation concealment; baseline characteristics were similar in all groups Performance: All three groups received doses via multiple-dose dry powder inhaler Detection: Details on the blinding were not given Attrition: 19.9% Pbo, 17.8% 200 µg, 12.6% 400 µg **External Validity:** Recruitment: Patients were evaluated for eligibility at screening and at baseline before randomization Patient Characteristics: Baseline characteristics were similar across all groups Setting: There was a two week run in period, and the study was conducted in an outpatient setting Outcomes: Patients were instructed to take their medications between 8-10am and 8-10pm. Efficacy and safety of patients were evaluated at study visits at week 1,4,8, and 12. Limited evidence fo patient-orientated outcomes, data in patients with less severe disease, and data comparing aclidinium to tiotropium or long acting beta2 agonists.

References:

1. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *The Lancet*. 2012;379(9823):1341–1351.

2. Hvidsten SC, Storesund L, Wentzel-Larsen T, Gulsvik A, Lehmann S. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. *Clin Respir J*. 2010;4(1):13–21.

3. GOLD_Report_2011_Feb21.pdf.

4. Aclidinium prescribing info.pdf.

5. FDA Summary Review.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000SumR.pdf. Accessed November 21, 2012.

6. Jones PW, Rennard SI, Agusti A, et al. Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. *Respiratory research*. 2011;12(1):55.

7. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: The ATTAIN study. *European Respiratory Journal*. 2012. Available at: http://erj.ersjournals.com/content/early/2012/03/22/09031936.00225511.short. Accessed November 21, 2012.

8. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Gil EG, Caracta CF. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2012;9(2):90–101.

9. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *European Respiratory Journal*. 2008;31(2):416–469.

Author: Brandy Fouts, Pharm.D.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Parameter	Result
Bioavailability	~6% (following inhalation)
Distribution	Vd of 300L following intravenous administration of 400μg
Elimination	Clearance 170 L/h, 1% excreted unchanged in the urine; after administration to healthy volunteers 54-65% of radioactivity was excreted in urine and 20-33% excreted in feces
Half-Life	5-8 hours
Metabolism	Hydrolysis both chemically and enzymatically by esterases. Not expected to alter disposition of medications, which use the CYP450 enzymes for metabolism.

DOSE & AVAILABILITY

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
400mcg	Inhalation	Twice daily	400μg	No adjustments	No adjustments	Not approved	Refer to adult dosing	

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): There are no REMS programs, black box warnings, or contraindications identified for aclidinium bromide.

Warnings and Precautions:

- *Not for acute use:* Aclidinium is intended for use as a maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy).
- *Paradoxical bronchospasm:* Inhaled medicines, like aclidinium, may cause paradoxical bronchospasm. If this occurs, treatment should be stopped.
- *Worsening of narrow-angle glaucoma:* Aclidinium should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.
- *Worsening of urinary retention:* Aclidinium should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of the signs or symptoms develop.
- *Immediate hypersensitivity reactions:* Immediate hypersensitivity reactions may occur after administration of aclidinium. If such a reaction occurs, therapy should be stopped and alternative treatments should be considered. Given the similar structural formulary of atropine to aclidinium, patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to aclidinium. In addition, aclidinium should be used with caution in patients with severe hypersensitivity to milk proteins.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Aclidinium may be confused with clidinium

Tudorza™ may be confused with Jolessa™, Lodosyn®, Taclonex®, Tekturna HCT®, Tekturna®, Tikosyn®, Tobrex®, Toradol®, Truvada®, Tubersol®, Zaditor®

Pressair™ may be confused with Provera®, Precose®, Primacor®

Author: Brandy Fouts, Pharm.D.

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

Abbreviated Drug Evaluation

Month/Year of Review: January 2013
End date of literature search: November 2012
Generic Name: Ipratropium/albuterol Inhaler
Brand Name (Manufacturer): Combivent Respimat® (Boehringer)

FDA Approved Indication: [1]
Ipratropium bromide/albuterol Respimat Inhalation Spray is a combination of an anticholinergic and beta-adrenergic indicated for patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. It is a propellant-free, non-CFC, inhaler that will be replacing the Combivent metered dose inhaler (MDI).

Conclusions:

- There is moderate quality evidence that ipratropium bromide/albuterol Respimat inhaler is non-inferior to ipratropium bromide/albuterol MDI on lung function as measured by improvement in FEV1 in the treatment of moderate to severe COPD.
- There is no evidence that the Respimat device offers any clinical advantage over other inhaled devices in the treatment of COPD.
- There is moderate quality evidence that ipratropium bromide/albuterol Respimat inhaler is generally well tolerated and has a similar safety profile to ipratropium bromide/albuterol MDI.
- Ipratropium/albuterol Respimat is a new version of Combivent without chlorofluorcarbons and will be replacing the previous MDI inhaler. It will be the only product available as of January 1, 2014.

Recommendations:

- Make the ipratropium/albuterol Respimat inhaler a preferred product to allow patients to conveniently switch from the MDI inhaler before January 1, 2014.

Background:

Drug classes available for the relief of airflow obstruction in patients with COPD include beta-2 adrenergic agonists, anticholinergic agents, combination products, and methylxanthines. Generic Combivent Inhalation Aerosol (ipratropium/albuterol sulfate) is currently a preferred inhaler on the Oregon Health Plan (OHP) preferred drug list (PDL). Combivent is a combination of a beta-2 adrenergic (albuterol) and anticholinergic (ipratropium). Ipratropium/albuterol metered-dose inhaler (MDI) is being phased out because it contains chlorofluorocarbons (CFCs), which are chemical compounds that decrease the ozone later. As a result, this will not be available after December 31, 2013. A new type of inhaler is the soft mist inhaler (SMI), which provides multi-dose medication using liquid formulations similar to that used in nebulizers and are propellant-fee. [1, 2] Respimat is currently the only soft mist inhaler (SMI) commercially available and as of January 1, 2014, ipratropium/albuterol Respimat will be the only Combivent product available. Both products have the same FDA-approved indications and

similar effectiveness. Main differences between the products include its general appearance, dosing, and the Respimat inhaler does not contain soy lecithin and therefore is not contraindicated in patients with soybean or peanut allergy.[3] The ipratropium/albuterol Respimat dose is one puff four times daily compared to the previous inhaler, which is two puffs four times daily.

A systematic review was conducted to evaluate the effectiveness of the Respimat inhaler when compared with other inhaler devices using the same drug for the treatment of COPD.[4] Randomized controlled trials were selected for inclusion and were assessed for quality using the Cochrane Collaboration approach and subsequently scored with a grade. The seven included trials were of high-quality. Two trials compared the Respimat inhaler versus the MDI inhaler (n=1421) and demonstrated no difference in risk of exacerbations (RR 1.20, 95% CI 0.95 to 1.51; p=0.12). Authors also concluded that there is currently no evidence to suggest that the Respimat inhaler device provides any additional clinical benefit to that provided by other devices. No differences were found in reported lung function or adverse events. [4]

Clinical Efficacy (see evidence table below):

The 12-week pivotal efficacy trial for ipratropium/albuterol Respimat was a randomized, double-blind, double-dummy study conducted in 1460 patients with moderate-severe COPD.[5] Patients were randomized to ipratropium/albuterol Respimat inhaler, ipratropium/albuterol CFC-MDI inhaler, or ipratropium alone Respimat inhaler. It was a designed as a non-inferiority study, using the MDI inhaler as the active comparator. Sixty-five percent of the patients were males. The mean age was approximately 64 years old, with an average duration of COPD of 8.5 years. The mean FEV1 % predicted was approximately 42%.[5]

The three co-primary endpoints in this study included FEV1 change from test-day baseline at day 85 for: 1) ipratropium/albuterol Respimat vs. ipratropium/albuterol MDI to demonstrate non-inferiority, 2) ipratropium/albuterol Respimat vs. ipratropium Respimat to show superiority, and 3) ipratropium/albuterol Respimat vs. ipratropium Respimat to show non-inferiority. The non-inferiority margin was 50 ml for the lower limit of the confidence interval. All three primary efficacy endpoints were met. [5] On test day 85, the ipratropium/albuterol Respimat inhaler group was non-inferior to the ipratropium/albuterol MDI group at 0-6 hours (FEV1 difference -0.003 L, 95% CI -0.022, 0.015). It was also found to be superior to the ipratropium alone Respimat inhaler (difference 0.0471, p<0.0001) at 0-4 hours, and demonstrated non-inferiority at 4-6 hours. [5] In addition, peak FEV1 and peak FEV1 response (secondary endpoints) were comparable between Respimat inhaler and MDI groups and superior to the ipratropium alone inhaler (p<0.0001) on all test days. [5]

Clinical Safety:

The most common adverse reactions in this 12-week trial included upper respiratory infection, nasopharyngitis, cough, bronchitis, headache, and dyspnea. The total incidence of adverse events was comparable across treatment groups and respiratory events were the most commonly reported. There were more patients who discontinued due to an adverse event in the MDI group compared to the Respimat group (6.9% vs. 3.7%; RR 0.6, 95% CI 0.3,1.0, P=0.05) and lower respiratory system disorders were the most frequent adverse event leading to discontinuation.[5] There was a higher frequency of serious adverse events in the MDI group compared to Respimat (6.7% vs. 3.5%). There was a total of 6 deaths that occurred during the study, however, none of these were considered related to study treatment. There were no clinically significant differences in vital signs for all treatment groups. According to the FDA medical reviewers, the pattern of serious adverse events and other adverse events did not raise any new safety concerns. [2]

There was also a long-term safety trial conducted that is unpublished at this time and therefore cannot be assessed for quality and risk of bias. It was a 48-week randomized, parallel, open-label safety trial (n=465) in patients with relatively stable moderate-severe COPD who were 40 years of age or older and had a smoking history.[2] Interim safety data at 24 weeks demonstrated that most adverse events were similar; however, cough occurred more frequently in the Respimat group (6.4%) compared to the MDI group (2.6%). Serious adverse events occurred in a total of 54 patients (11.6%) across all treatment groups and the frequency was similar across all groups. The most common serious adverse event was COPD exacerbation in all treatment groups. Fewer patients in the Respimat group withdrew from the study due to adverse events (5.7%) compared to the MDI group (6.5%).[2]

Author: Megan Herink, Pharm.D.

This study also measured patient acceptability using the Patient Satisfaction and Preference Questionnaire (PASAPQ) at 24 weeks. This is a validated tool for evaluating inhaler satisfaction. The PASAPQ score was significantly higher with ipratropium/albuterol Respimat compared to ipratropium/albuterol MDI aerosol for all evaluated time points through week 24 ($p<0.0001$). [2]

Although not an efficacy study, data showed that all three treatments increased FEV1 and FVC and there were no significant differences between the groups. [2]

Author: Megan Herink, Pharm.D.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Lung Function Measurements (FEV1, FVC)
3) COPD Exacerbations
4) Withdrawals due to adverse events

Primary Study Endpoint:

1) FEV1 change from baseline at day 85
   a. Non-inferiority of ipratropium/albuterol Respimat to MDI from 0 to 6 hours
   b. Superiority of ipratropium/albuterol Respimat to ipratropium Respimat from 0 to 4 hours
   c. Non-inferiority of ipratropium/albuterol Respimat to ipratropium Respimat from 4 to 6 hours

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)[3]	ARR/ NNT[4]	Safety Results (CI, p-values)	ARR/ NNH[4]	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns[5]
1.ZuWallack, et al. RCT, DB, DD, non-inferiority study	1. Combivent Respimat 2 Combivent MDI 3. Ipratropium Respimat Each administered four times daily. All provided with albuterol MDI to use as needed. 2 week run-in with ipratropium.	65% males, mean age 64, average duration of COPD 8.5 yrs, mean FEV1 42% Inclusion Criteria: >40 y/o, moderate-severe COPD, FEV1 ≤65%, smoking history of ≥10 pack-years Exclusion Criteria: Hypersensitivty to medications, elevated blood eosinophil count, respiratory infection within 6 weeks prior to screening, use of antihistamines, oral corticosteroids at unstable doses, use of beta-blockers, tricyclic antidepressants, or monoamine oxidase inhibitors less than 30 days before baseline.	1.486 2. 491 3. 483	Mean FEV1 on day 85: Respimat vs. MDI (non-inferiority) Resp:0.145 MDI; 0.149 Difference: -3 (95% CI -22, 15)	N/A	Withdrawals due to Adverse events: Resp 19 (3.9%) MDI: 34 (6.9%) Ipra: 35 (7.2%) Resp vs. MDI: RR 0.6 (95% CI 0.3,1.0) P=0.05 COPD exacerbations: Resp 72 (14.8%) MDI: 64 (13%) Ipra: 50 (10.4%) Resp vs. MDI: RR 1.1 (95% CI 0.8, 1.6) P=0.4	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: No specific details on randomization process or concealment of allocation. Performance: Baseline characteristics were comparable among groups. Double-dummy design prevented investigators and patients from differentiating drug from placebo. Detection: Unknown if outcome assessors blinded. Attrition: Total attrition 12.6 % ipratropium Respimat, 11.2% Combivent MDI, 9.9% Combivent Respimat. More discontinuation due to non-compliance in Respimat groups compared to MDI. **External Validity:** Recruitment: No information Patient Characteristics: Majority of subjects were white males. Patients with narrow-angle glaucoma, symptomatic prostatic hypertrophy or bladder-neck obstruction were excluded from the trial. Setting: Multinational (13 countries), multi-center (179 centers). Outcomes: Non-inferiority study; not designed to compare efficacy or harms.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial,, DD = double-dummy [2]**Drug Regimens:** Combivent = ipratropium/albuterol, MDI=multi-dose inhaler [3]**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, ARI = absolute risk increase [4]**NNT/NNH** are reported only for statistically significant results [5]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Author: Megan Herink, Pharm.D.

References:

1. Combivent®. Respimat® (ipratropium bromide and albuterol) prescribing information; xxx2011.

2. Center for Drug Evaluation and Research. Medical Review(s) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021747Orig1s000MedR.pdf.

3. PL Detail-Document. New Formulation: Combivent Respimat. Pharmacist's Letter/Prescriber's Letter. September 2012. Available at: http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PL&pt=6&fpt=31&dd=280909&pb=PL&searchid=39088946.

4. Ram FSF, Carvallho CR, White J. Clinical effectiveness of the Respimat inhaler device in managing chronic obstructive pulmonary disease: evidence when compared with other handheld inhaler devices. *Int J Chron Obstruct Pulmon Dis*. 2011;6:129–139.

5. Zuwallack R, De Salvo MC, Kaelin T, et al. Efficacy and safety of ipratropium bromide/albuterol delivered via Respimat inhaler versus MDI. *Respir Med*. 2010;104(8):1179–1188.

Author: Megan Herink, Pharm.D.

Appendix 1: Specific Drug Information

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose
One inhalation	Inhaled	Four Times Daily	20 mcg ipratropium and 100 mcg albuterol per actuation	Has not been studied.	Has not been studied.	Has not been established.	No dosage adjustment warranted.

Other Dosing Considerations:

The inhaler must be assembled by inserting the cartridge into inhaler. Product requires priming prior to first use by actuating the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. If the inhaler is not used for more than 3 days, actuate the inhaler once to prepare it for use. If the inhaler has not been used for more than 21 days, repeat the same process used for first time use. The discard date is 3 months from the date the cartridge is inserted into the inhaler.

The device has a dose indicator that uses a color-coded scale marked in increments of 30 doses. The indicator provides an approximation of how many doses are left, but does not count individual doses. When the pointer enters the red area of the scale, there is enough medicine for 7 days. Once the dose indicator has reached the end of the scale, all 120 puffs have been used, the inhaler locks automatically. At this point, the base cannot be turned any further.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Contraindications: Hypersensitivity to any of the ingredients or to atropine or any of its derivatives

Warnings and Precautions:

Paradoxical bronchospasm: Discontinue immediately if occurs

Patients with cardiovascular system disorders: Use with caution because of beta-adrenergic stimulation.

Ocular effects: Advise patients to avoid spraying into eyes and to contact a physician if blurred vision, halos, or other visual disturbances occur.

Urinary retention: Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction

Coexisting conditions: Use with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus.

Author: Megan Herink, Pharm.D.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2012
PDL Classes: Macrolides and Related Antibiotics

Date of Last Review: 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: AZITHROMYCIN, CLARITHROMYCIN, ERYTHROMYCIN BASE, ERYTHROMYCIN ETHYLSUCCINATE, ERYTHROMYCIN
- Non Preferred Agents: CLARITHROMYCIN ER, DIRITHROMYCIN (DYNABAC®), TELITHROMYCIN (KETEK®), FIDAXOMICIN (DIFICID®)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Recommend inclusion of at least one medication from this group. Consider including Azithromycin or Clarithromycin for Mycobacterium Avium Complex coverage.
- Telithromycin use is limited, not considered first line therapy; consider PA criteria to limit telithromycin to use for multi-drug resistant community acquired pneumonia and allowing bridge therapy for hospitalized patients on discharge.

Methods:

A Medline OVID search was conducted with the following search terms: erythromycin, clarithromycin, azithromycin, telithromycin, acne vulgaris, endocarditis, sexually transmitted disease, chlamydia, gonorrhea, intestinal infectious disease, infection of skin, infection of subcutaneous tissue, soft tissue infection, Legionnaires Disease, Listeriosis, urethritis, Pertussis, respiratory tract infection, syphilis, community acquired pneumonia, Mycobacterium Avium infection, Duodenal Ulcer Disease, Helicobacter Pylori, gastrointestinal tract infection, COPD, otitis media, conjunctivitis, sinusitis, cervicitis, Pelvic Inflammatory Disease, diarrhea, septicemia, bacterial vaginosis, endometritis, peritonitis, Anthrax, Bartonellosis, Legionella pneumonia, Lyme Disease, Babesiosis, and Cystic Fibrosis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to October week 2 2012.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

New Trials:

A total of 210 citations resulted from the initial MEDLINE search. After review of titles and abstracts for inclusion, no relevant head-to-head clinical trials were identified. Articles were excluded due to the wrong study design (observational), comparator (placebo or other antibiotic class), or outcome (non-clinical).

New drugs:

Dificid (fidaxomicin)[1] is a new macrolide antibiotic approved in May 2011 for the treatment of Clostridium difficile associated diarrhea. Dificid was reviewed for the Oregon P & T Committee in April 2012 and made non-preferred with prior authorization criteria for use.[2]

New Formulations/Indications:
A new packaging combination of amoxicillin, clarithromycin, and omeprazole was approved in 2010. All three medications are packaged together to treat *Helicobacter pylori* infections in patients with current or former Duodenal Ulcer Disease.[3] The new packaging appears to be an attempt to increase patient convenience; there is no evidence of clinical benefit or advantage over currently available formulations.

New FDA safety alerts:
In May 2012, the FDA released a safety alert[4] regarding systemic azithromycin use. An observational study[5] published in the New England Journal of Medicine showed a significant increase in the risk of cardiovascular death in patients treated with azithromycin as opposed to patients treated with either amoxicillin, ciprofloxacin or no drug at all. The FDA acknowledged the association of macrolide use and cardiovascular effects, specifically QT prolongation. In 2011, a warning concerning the risk of QT prolongation was added to all systemic erythromycin[6], clarithromycin[7] and azithromycin[4] products' labeling. The safety alert recommends that Healthcare professionals should be aware of the potential for QT interval prolongation and heart arrhythmias when prescribing or administering macrolides.

New Systematic Reviews:
Three new or updated, relevant systematic reviews were identified.

A 2011 meta-analysis attempted to compare and evaluate the efficacy and safety of azithromycin and clarithromycin in cystic fibrosis (CF) patients. The primary efficacy outcome was the impact on the deterioration of lung function measured by changes in FEV_1; safety outcomes included adverse events and mortality. Azithromycin treatment showed a significant increase in FEV_1% (3.22%; 95% CI = 1.38 to 5.06) when compared with placebo. Adverse events were not significantly different between the azithromycin groups and the placebo group. Only one small trial with clarithromycin was included making comparisons with azithromycin difficult. [8]

A Cochrane review looking at pertussis treatment regimens was updated in 2011. In treating *Bordetella pertussis*, short-term antibiotics (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) were as effective as long-term (erythromycin for 10 to 14 days) (RR 1.01; 95% CI 0.98 to 1.04), but had fewer side effects (RR 0.66; 95% CI 0.52 to 0.83). There were no differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. Side effects were not compared with one antibiotic to another.[9]

A Cochrane review updated early 2012, looked at comparative treatment of genital chlamydial infections in pregnant women. Patients treated with amoxicillin, erythromycin, clindamycin or azithromycin were included. For the outcome microbiological cure, clindamycin versus erythromycin was non-significant (OR 0.42; 95% CI 0.11 to 1.68). In comparing azithromycin with erythromycin, erythromycin was more likely achieve a microbiological cure (OR 0.38; 95% CI 0.19 to 0.74). Amoxicillin was not significantly more effective than erythromycin in achieving microbiological cure (OR 0.54, 95% CI 0.28 to 1.02) but was better tolerated than erythromycin (OR 0.16; 95% CI 0.09 to 0.30).[10]

Guidelines:
Updated guidelines for COPD from the American Thoracic Society[11] and Global Initiative for Chronic Obstructive Lung Disease[12] were reviewed; as was the updated chlamydia guideline[13] from the Centers for Disease Control. Updated treatment guidelines for bacterial rhino-sinusitis[14], community acquired pneumonia[15], Lyme Disease and Babesiosis[16], and acute uncomplicated cystitis[17] from the Infectious Disease Society of America were also evaluated. No changes regarding the use of macrolides were found.

Recommendations:
- There is insufficient evidence from head-to-head studies that consistently demonstrate the superiority of one macrolide over another. No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

1. Anon. Dificid (fidaxomicin) Prescribing Information. *Optimer Pharmaceuticals; San Diego CA*. 2011.

2. Oregon P&T Minutes. Oregon P & T Minutes 2012_04_26_PT_Minutes.pdf. Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/meeting. Accessed October 22, 2012.

3. Anon. Omeprazole, Clarithromycin, and Amoxicillin Prescribing Information. *DAVA Pharmaceuticals; Fort Lee, NJ*. 2010. Available at: http://drugs-about.com/pdf/omeprazole-apotex/omeprazole-apotex.pdf. Accessed October 21, 2012.

4. FDA. Safety Alerts for Human Medical Products > Zithromax (azithromycin): FDA Statement on risk of cardiovascular death. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm304503.htm. Accessed October 22, 2012.

5. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the Risk of Cardiovascular Death. *New England Journal of Medicine*. 2012; 366(20):1881–1890.

6. FDA. Safety Information > EES (erythromycin ethylsuccinate) Granules for oral suspension, Eryc (erythromycin delayed-release) capsules, Ery-Ped liquid and PCE (erythromycin particles in tablets) 333 mg and 500 mg film coated tablets. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm294615.htm. Accessed October 22, 2012.

7. FDA. Safety Information > Biaxin Filmtab (clarithromycin tablets, USP), Biaxin XL Filmtab (clarithromycin extended-release tablets), Biaxin Granules (clarithromycin for oral suspension, USP). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258816.htm. Accessed October 22, 2012.

8. Cai Y, Chai D, Wang R, Bai N, Liang B-B, Liu Y. Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review. *Journal of Antimicrobial Chemotherapy*. 2011; 66(5):968–978.

9. Altunaiji SM, Kukuruzovic RH, Curtis NC, Massie J. Antibiotics for whooping cough (pertussis). In: The Cochrane Collaboration, Altunaiji SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007. Available at: http://doi.wiley.com/10.1002/14651858.CD004404.pub3. Accessed October 22, 2012.

10. Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. In: The Cochrane Collaboration, Henderson S, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 1998. Available at: http://doi.wiley.com/10.1002/14651858.CD000054. Accessed October 22, 2012.

11. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann. Intern. Med.* 2011; 155(3):179–191.

12. Rosin R, Anzueto A, Bourbeau J, deGuia T, Hui D. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Revised 2011. GOLD_Report_2011Dec30.pdf. 2011. Available at: http://www.goldcopd.org. Accessed October 22, 2012.

13. Geisler WM. Diagnosis and management of uncomplicated Chlamydia trachomatis infections in adolescents and adults: summary of evidence reviewed for the 2010 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Clin. Infect. Dis.* 2011;53 Suppl 3:S92–98.

14. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin. Infect. Dis.* 2012; 54(8):e72–e112.

15. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2011;53(7):e25–76.

16. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2006;43(9):1089–1134.

17. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infectious Diseases*. 2011;52(5):e103–e120.

Appendix 1

Systematic Review Abstracts

Cai Y, Chai D, Wang R, Bai N, Liang B-B, Liu Y. Effectiveness and safety of macrolides in cystic fibrosis patients: a meta-analysis and systematic review. *Journal of Antimicrobial Chemotherapy*. 2011;66(5):968–978.

Objectives To evaluate the efficacy and safety of macrolides in cystic fibrosis (CF).

Methods Randomized controlled trials (RCTs) of macrolides for the treatment of CF published in PubMed, the Cochrane Library and Embase were searched. Application of inclusion and exclusion criteria, data extraction, and assessment of methodological quality were independently performed in duplicate. The primary efficacy outcome was the impact on the deterioration of lung function (changes in FEV_1 and FVC). Safety outcomes included adverse events and mortality.

Results Eight RCTs (seven with azithromycin and one with clarithromycin) were found in the systematic review and six RCTs with azithromycin (654 patients) were included in the meta-analysis. Azithromycin treatment showed a significant increase in FEV_1% (3.22%, 95% CI = 1.38–5.06, P = 0.0006, I^2 = 0%) and FVC% (3.23%, 95% CI = 1.62–4.85, P < 0.0001, I^2 = 0%) compared with placebo. In individuals with baseline *Pseudomonas aeruginosa* colonization, both FEV_1% (4.80%, 95% CI = 1.66–7.94, P = 0.003, I^2 = 42%) and FVC% (4.74%, 95% CI = 1.92–7.57, P = 0.001, I^2 = 0%) increased significantly. The incidence rates of the main side effects (cough, headache, abdominal pain, vomiting, nausea and diarrhoea) were not significantly different between the azithromycin-treated group and the placebo group. The RCT of clarithromycin, involving 18 patients, showed its effects on clinical improvement; however, the small sample size made comparisons with azithromycin difficult.

Conclusions Long-term use of azithromycin can improve lung function, especially for *P. aeruginosa*-colonized CF patients. There was no evidence of increased adverse events with azithromycin. More data are needed to verify the best azithromycin regimen and to evaluate other macrolides in CF patients.

Altunaiji SM, Kukuruzovic RH, Curtis NC, Massie J. Antibiotics for whooping cough (pertussis). In: The Cochrane Collaboration, Altunaiji SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.

Background Whooping cough is a highly contagious respiratory disease. Infants are at highest risk of severe disease and death. Erythromycin for 14 days is currently recommended for treatment and contact prophylaxis but its benefit is uncertain.

Objectives To assess the risks and benefits of antibiotic treatment of and contact prophylaxis against whooping cough in children and adults.

Search methods We searched the Cochrane Central Register of Controlled Trials (CENTRAL Issue 4, 2010), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, the Database of Abstracts of Reviews of Effects (DARE Issue 4, 2010), MEDLINE (1966 to January Week 1, 2011) and EMBASE (1974 to 18 January 2011).

Selection criteria Randomised controlled trials (RCTs) and quasi-RCTs of antibiotics for treatment of and contact prophylaxis against whooping cough in children and adults.

Data collection and analysis Three to four review authors independently extracted data and assessed the quality of each trial.

Main results Thirteen trials with 2197 participants met the inclusion criteria: 11 trials investigated treatment regimens; two investigated prophylaxis regimens. The quality of the trials was variable. For eradicating *Bordetella pertussis* (*B. pertussis*) from the nasopharynx, short-term antibiotics (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) were as effective as long-term (erythromycin for 10 to 14 days) (risk ratio (RR) 1.01; 95% confidence interval (CI) 0.98 to 1.04), but had fewer side effects (RR 0.66; 95% CI 0.52 to 0.83). Trimethoprim/sulphamethoxazole for seven days was also effective. Nor were there differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. For preventing infection by treating contacts older than six months of age, antibiotics did not significantly improve clinical symptoms, nor the number of cases developing culture-positive *B.pertussis*. Side effects were reported with antibiotics and they varied from one antibiotic to another.

Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. In: The Cochrane Collaboration, Henderson S, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 1998.

Background Chlamydia trachomatis is a sexually transmitted infection. Mother-to-child transmission can occur at the time of birth and may result in ophthalmia neonatorum or pneumonitis in the newborn.

Objectives The objective of this review was to assess the effects of antibiotics in the treatment of genital infection with Chlamydia trachomatis during pregnancy with respect to neonatal and maternal morbidity.

Search methods We searched the Cochrane Pregnancy and Childbirth Group's Trials Register and added the results to Studies awaiting classification (September 2006).We updated this search on 3 January 2012 and added one additional trial report to the awaiting classification section.

Selection criteria Randomised trials of any antibiotic regimen compared with placebo or no treatment or alternative antibiotic regimens in pregnant women with genital Chlamydia trachomatis infection.

Data collection and analysis Two review authors assessed trial quality and extracted data independently. Study authors were contacted for additional information.

Main results Eleven trials were included. Trial quality was generally good. Amoxicillin appeared to be as effective as erythromycin in achieving microbiological cure (odds ratio 0.54, 95%confidence interval 0.28 to 1.02). Amoxicillin was better tolerated than erythromycin (odds ratio 0.16, 95% confidence interval 0.09 to 0.30). Clindamycin and azithromycin also appear to be effective, although the numbers of women included in trials are small.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2013 **Date of Last Review:** November 2009
PDL Classes: Fluoroquinolones, Oral **Source Document:** Provider Synergies

Current Status of PDL Class:

- Preferred Agents: Ciprofloxacin suspension and tablets, levofloxacin solution and tablets, norfloxacin
- Non Preferred Agents: Ciprofloxacin ER (CIPRO XR®, PROQUIN XR®), moxifloxacin (AVELOX®), ofloxacin, gemfloxacin (FACTIVE®)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend inclusion of at least one medication with pseudomonas coverage and at least one "respiratory" quinolone (gemifloxacin, levofloxacin, moxifloxacin).

Methods:

A Medline OVID search was conducted with the following search terms: fluoroquinolones, ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, prostatitis, bronchitis, COPD, COPD exacerbation, sexually transmitted disease, chlamydia, gonorrhea, osteitis, osteomyelitis, otitis externa, typhoid fever, pyelonephritis, urinary tract infection, enterocolitis, tuberculosis, mycobacterium infection, chancroid, cholera, cholangitis, Crohn's disease, gastroenteritis, endocarditis, meningococcal infection, peritonitis, Plague, Pseudomonas, pneumonia, intestinal infectious disease, epididymitis, urethritis, respiratory tract infection, community acquired pneumonia, Mycobacterium Avium infection, Helicobacter Pylori, gastrointestinal tract infection, otitis media, sinusitis, Pelvic Inflammatory Disease, diarrhea, peritonitis, Anthrax, and Cystic Fibrosis. The search was limited to English language articles of controlled trials conducted on humans published from 2009 to October week 4 2012.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

New Trials:

A total of 201 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or other antibiotic class), or outcome (non-clinical). After a review of titles and abstracts for inclusion, five relevant head-to-head trials were identified. See Appendix 1 for complete trial abstracts.

Two trials examined the use of moxifloxacin for uncomplicated Pelvic Inflammatory Disease (PID). Heystek and Ross[1] randomized 434 women to moxifloxacin or combination doxycycline, metronidazole and ciprofloxacin for 14 days. The results of this double-blind, multi-center trial showed moxifloxacin was non-inferior to the combination regimen with the overall clinical success rates at 2–14 days post-therapy were 96.6% (moxifloxacin) and 98.0% (comparator) (95%CI: −4.5, 1.6). Clinical success was not defined. Only the abstract was available for review and the quality of the trial was therefore not evaluated.

Judlin et al[2] also examined moxifloxacin for uncomplicated PID. This fair quality randomized, double-blind, multi-center trial evaluated moxifloxacin versus levofloxacin plus metronidazole in 460 women for 14 days. The primary outcome was

clinical response 7–14 days after the last dose. Clinical response was defined as a reduction in the tenderness score, apyrexia and WBC <10 500/mm^3. Moxifloxacin was found to be non-inferior to levofloxacin plus metronidazole: 78.4% (moxifloxacin) and 81.6% (comparator) (95% CI: −10.7, 4.9). Both treatments were considered well-tolerated with nausea as the most common side effect for both groups.

Marom et al[4] conducted an open label phase II trial comparing two ciprofloxacin formulations for acute otitis media (AOE) in adults. The fair quality study randomized 64 patients to either foam-based or solution-based ciprofloxacin; all patients received medication twice daily for seven days. The primary efficacy outcome was infection cure by day 8 to 14. All patients included in the analysis achieved this outcome (defined as improvement or resolution of symptoms). No significant differences were found between treatments.

New drugs, formulations, or indications:
None

New FDA safety alerts:
No new safety alerts were released since 2009; however the FDA required several safety label changes for fluoroquinolones. In 2011, the FDA added the warning for potential increased intracranial pressure for ciprofloxacin[5] and gemifloxacin[6]. In 2012, moxifloxacin[7] labeling was altered to include a warning for increased risk of developing peripheral neuropathy. Lastly, the FDA added a warning to all systemic fluoroquinolones[8] concerning risk for exacerbation of Myasthenia Gravis in patients with a history of the condition.

In 2012, a case-control study published in the Journal of the American Medical Association found that patients who take fluoroquinolones are at an increased risk of retinal detachment, although the absolute risk for developing the condition remains small.[9] Absolute increase in risk of retinal detachment was 4 per 10,000 person-years.

New Systematic Reviews: (Appendix 2)

A new systematic review by Ziganshina et al[10] evaluated the use of fluoroquinolones for tuberculosis (TB) for the Cochrane Collaboration. This systematic review included 11 randomized and quasi-randomized trials with 1,514 participants. Study quality varied greatly; allocation concealment was described in only one trial, and blinding was either unclear or not done in seven of the trials. The primary outcome was cure of disease: defined as a negative sputum culture at both week eight and the end of treatment. Three interventions were studied. The first intervention looked at the efficacy of a fluoroquinolone (ciprofloxacin, moxifloxacin or ofloxacin) substituted into the TB regimen for rifampin, ethambutol or pyrazinamide plus ethambutol. No difference was found in either the rate of treatment cure or failure; however, use of ciprofloxacin or ofloxacin was associated with a higher incidence of relapse (RR 7.17, 95% CI: 1.33, 38.58). The second intervention compared standard TB treatment with and without the addition of levofloxacin. The third intervention compared the efficacy of substituting levofloxacin or ofloxacin for rifampin in TB treatment. No difference was found in treatment cure or failure between the two fluoroquinolones. The authors concluded although fluoroquinolones have anti-tubercular activity, they should not be substituted for standard TB treatment.

In another Cochrane Collaboration systematic review, Rafalsky et al[11] examined the use of fluoroquinolones for uncomplicated cystitis in women. The objective of the analysis was to compare efficacy, safety and tolerability amongst fluoroquinolones. This systematic review included 11 randomized and quasi-randomized trials with 7,535 women aged 16 and older. Study quality was mostly good; allocation concealment was described in all but one trial, seven trials described the randomization process and double-blinding was explicitly stated for ten of the trials. No trial used the same comparators and many fluoroquinolones included are not available in the US. The authors felt that none of the quinolones showed any advantage for efficacy in treating cystitis. Differences were seen for safety and tolerability. One study showed ofloxacin was more likely to cause adverse events (RR 0.8, 95% CI: 0.65, 0.99) than ciprofloxacin. In another study, adverse events were higher for ofloxacin (RR 0.45, 95% CI 0.22, 0.93) than levofloxacin. There was insufficient evidence to recommend one fluoroquinolone over another.

Guidelines:
Updated guidelines for sexually transmitted infections[12] from the Center of Disease Control (CDC) were reviewed for such relevant topics as chlamydia, pelvic inflammatory disease, cystitis, urethritis, and epididymitis. The World Health Organization updated drug-resistant tuberculosis[13] recommendations were also reviewed for any changes. As was the updated joint guideline from the CDC, Infectious Disease Society of America (IDSA), and National Institute of Health (NIH) for treatment of opportunistic infections in HIV patients[14]. Updated treatment guidelines from the IDSA were also evaluated for bacterial rhino-sinusitis[15]; community acquired pneumonia[16]; management of intra-abdominal infections[17]; urinary tract infection from catheters[18]; febrile neutropenia[19]; and acute uncomplicated cystitis and pyleonephritis[20]. No changes regarding the use of fluoroquinolones were found.

Recommendations:

- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

1. Heystek, M. & Ross, J. D. C. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. *Int J STD AIDS* **20**, 690–695 (2009).
2. Judlin, P. *et al.* Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. *BJOG: An International Journal of Obstetrics & Gynaecology* **117**, 1475–1484 (2010).
3. Shah, V. M. *et al.* Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers. *Cornea* **29**, 751–757 (2010).
4. Marom, T. *et al.* Comparison of safety and efficacy of foam-based versus solution-based ciprofloxacin for acute otitis externa. *Otolaryngol Head Neck Surg* **143**, 492–499 (2010).
5. Drug Safety Labeling Changes > Cipro (ciprofloxacin hydrochloride). *www.fda.gov* at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm161806.htm>
6. Safety Information > Factive (gemifloxacin mesylate) Tablet. at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm279846.htm>
7. Safety Information > Avelox (Moxifloxacin Hydrochloride) Tablet and Injection. at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319318.htm>
8. Safety Information > Risk of fluoroquinolone-associated Myasthenia Gravis Exacerbation February 2011 Label Changes for Fluoroquinolones. *www.fda.gov* at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm247115.htm>
9. Etminan, M., Forooghian, F., Brophy, J. M., Bird, S. T. & Maberley, D. Oral fluoroquinolones and the risk of retinal detachment. *JAMA* **307**, 1414–1419 (2012).
10. Ziganshina, L. E. & Squire, S. B.in *Cochrane Database of Systematic Reviews* (The Cochrane Collaboration & Ziganshina, L. E.) (John Wiley & Sons, Ltd, 2008).at <http://doi.wiley.com/10.1002/14651858.CD004795.pub3>
11. Rafalsky, V. V., Andreeva, I. V. & Rjabkova, E. L.in *Cochrane Database of Systematic Reviews* (The Cochrane Collaboration & Rafalsky, V. V.) (John Wiley & Sons, Ltd, 2006).at <http://doi.wiley.com/10.1002/14651858.CD003597.pub2>
12. Workowski, K. A. & Berman, S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* **59**, 1–110 (2010).
13. Falzon, D. *et al.* WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur. Respir. J.* **38**, 516–528 (2011).
14. Kaplan, J. E. *et al.* Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* **58**, 1–207; quiz CE1–4 (2009).
15. Chow, A. W. *et al.* Executive Summary: IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. *Clinical Infectious Diseases* **54**, 1041–1045 (2012).
16. Bradley, J. S. *et al.* The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases* **53**, e25–e76 (2011).
17. Solomkin, J. S. *et al.* Diagnosis and Management of Complicated Intra- abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases* **50**, 133–164 (2010).
18. Hooton, T. M. *et al.* Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases* **50**, 625–663 (2010).
19. Freifeld, A. G. *et al.* Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* **52**, e56–e93 (2011).
20. Gupta, K. *et al.* International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical Infectious Diseases* **52**, e103–e120 (2011).

Appendix 1

Randomized Clinical Trial Article Abstracts

Judlin, P. *et al.* Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. *BJOG: An International Journal of Obstetrics & Gynaecology* 117, 1475–1484 (2010).

Objective**:** To evaluate the efficacy and safety of moxifloxacin versus levofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease (uPID) in Asia.

Design: Prospective, randomised, double-blind, double-dummy, parallel-group study.

Setting: Multicentre, multinational study in the inpatient and/or outpatient setting.

Population**:** Women (aged ≥18 years) with uPID (defined as PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination) and not requiring intravenous treatment.

Methods**:** Women received a 14-day course of either oral moxifloxacin, 400 mg once daily, or oral levofloxacin, 500 mg once daily, plus oral metronidazole, 500 mg twice daily. Additionally, a single dose of ceftriaxone, 250 mg intramuscularly, was administered to women who had a positive screening test for *Neisseria gonorrhoeae*.

Main outcome measures**:** The primary measure of efficacy was clinical response at test-of-cure (TOC) (7–14 days after the last dose of study drug) in the per-protocol population. Noninferiority of moxifloxacin to the comparator regimen was demonstrated if lower limit of 95% CI was >−15%. Other measures were clinical response during therapy and at 4-week follow up, microbiological response at TOC, and safety.

Results: A total of 460 women were randomised to the study. For the primary measure of efficacy (clinical cure at TOC), moxifloxacin was noninferior to levofloxacin plus metronidazole (moxifloxacin: 152/194, 78.4%; comparator 155/190, 81.6%; 95% CI −10.7 to +4.9). The most commonly isolated pathogens at baseline included *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Escherichia coli*, *Staphylococcus aureus*, *Peptostreptococcus* spp., *Proteus mirabilis*, *Streptococcus agalactiae* and *Klebsiella pneumoniae*. Bacteriological success rates were high and comparable between treatment arms (microbiologically valid populations, moxifloxacin 27/30, 90.0%; comparator 22/26, 84.6%; 95% CI −12.7 to +20.3). Both treatments were well tolerated.

Conclusions: Moxifloxacin monotherapy, 400 mg once daily for 14 days, is an effective and well-tolerated oral treatment for women with uPID.

Heystek, M. & Ross, J. D. C. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. *Int J STD AIDS* 20, 690–695 (2009).

This multicentre, double-blind study was undertaken to demonstrate non-inferiority of once-daily oral moxifloxacin compared with combination therapy in the management of acute, uncomplicated pelvic inflammatory disease (PID). Women aged ≥18 years with PID were randomized to receive moxifloxacin (400 mg once daily) for 14 days or comparator treatment (doxycycline [100 mg twice daily] plus metronidazole [400 mg three times daily] for 14 days, plus one single 500-mg ciprofloxacin dose). Of the 434 valid per protocol (PP) patients, the overall clinical success rates at 2–14 days post-therapy were 96.6% (moxifloxacin) and 98.0% (comparator); moxifloxacin was non-inferior to the comparator regimen both in the PP (95% confidence interval [CI]: −4.5, 1.6) and intent-to-treat (95% CI: −5.8, 6.9) populations. Clinical success rates at 21–35 days post-therapy were 93.8% (166/177; data missing for 47 patients) for moxifloxacin and 91.3% (147/161; data missing for 37 patients) for the comparator. Bacteriological success rates at 2–14 days post-therapy were 92.5% (moxifloxacin) and 88.2% (comparator). Once-daily dosing and proven efficacy suggest that moxifloxacin may be of value in acute, uncomplicated PID.

Marom, T. *et al.* Comparison of safety and efficacy of foam-based versus solution-based ciprofloxacin for acute otitis externa. *Otolaryngol Head Neck Surg* 143, 492–499 (2010).

Objective**:** To compare and evaluate the efficacy and safety of a foam-based antibiotic formulation in the treatment of acute otitis externa (AOE) with the more conventional solution-based formulation.

Study Design**:** Phase 2, open-label, randomized controlled trial. Setting**:** Multicenter. Subjects and methods: Sixty-three eligible adult patients with unilateral AOE were randomly assigned to one of two treatment groups: an experimental 0.3 percent foam-based ciprofloxacin, (FoamOtic Cipro) or 0.3 percent solution-based ciprofloxacin (Ciloxan). All patients received the same dose regime (twice daily for 7 days). The primary efficacy variable was response to therapy (cure) in the test-of-cure visit. Secondary variables included improvement of the disease symptoms otalgia, tenderness, edema, and otorrhea.

Results: Sixty-four patients were enrolled in the study. Seven patients were excluded from the per-protocol analysis due to major deviations from the protocol. Per-protocol analysis (n = 57) showed that cure was achieved in all the patients (P = 1.000). No significant differences were found between groups for symptomatic relief, resolution of otic discharge, or onset of pain reduction. Both treatments were found to be highly efficacious and safe, demonstrating the noninferiority of the experimental drug.

Conclusion: Foam-based ciprofloxacin is a safe and an effective new treatment for AOE.

Appendix 2

Abstracts for Meta Analyses

Rafalsky, V. V., Andreeva, I. V. & Rjabkova, E. L. Quinolones for uncomplicated acute cystitis in women. *Cochrane Database of Systematic Reviews* (2006).at <http://doi.wiley.com/10.1002/14651858.CD003597.pub2>

Background: Fluoroquinolones are sometimes used to treat multiple-drug-resistant and drug-sensitive tuberculosis. The effects of fluoroquinolones in tuberculosis regimens need to be assessed.

Objectives: To assess fluoroquinolones as additional or substitute components to antituberculous drug regimens for drug-sensitive and drug resistant tuberculosis.

Search methods: In July 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, LILACS, Science Citation Index, Database of Russian Publications, and *meta*Register of Controlled Trials. We also scanned reference lists of all identified studies and contacted researchers.

Selection criteria: Randomized controlled trials of antituberculous regimens containing fluoroquinolones in people diagnosed with bacteriologically positive (sputum smear or culture) pulmonary tuberculosis.

Data collection and analysis: Two authors independently applied inclusion criteria, assessed the risk of bias in the trials, and extracted data. We used risk ratio (RR) for dichotomous data, mean difference (MD) for continuous data (both with 95% confidence intervals (CI)), and the random-effects model if we detected heterogeneity and it was appropriate to combine data.

Main results: Eleven trials (1514 participants) met the inclusion criteria. No statistically significant difference was found in trials substituting ciprofloxacin, ofloxacin or moxifloxacin for first-line drugs in relation to cure (416 participants, 3 trials), treatment failure (388 participants, 3 trials), or clinical or radiological improvement (216 participants, 2 trials). Substituting ciprofloxacin into first-line regimens in drug-sensitive tuberculosis led to a higher incidence of relapse (RR 7.17, 95% CI 1.33 to 38.58; 384 participants, 3 trials) and longer time to sputum culture conversion (MD 0.50 months, 95% CI 0.18 to 0.82; 168 participants, 1 trial), although this was confined to HIV-positive participants. Substituting for ethambutol in first-line regimens led to a higher incidence of total number of adverse events (RR 1.34, 95% CI 1.05 to 1.72; 492 participants, 2 trials). Adding or substituting levofloxacin to basic regimens in drug-resistant areas had no effect. A comparison of sparfloxacin versus ofloxacin added to regimens showed no statistically significant difference in cure (184 participants, 2 trials), treatment failure (149 participants, 2 trials), or the total number of adverse events (253 participants, 3 trials).

Authors' conclusions: Only ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin and moxifloxacin have been tested in randomized controlled trials for treating tuberculosis. We cannot recommend ciprofloxacin in treating tuberculosis. Trials of newer fluoroquinolones for treating tuberculosis are needed and are ongoing. No difference has been demonstrated between sparfloxacin and ofloxacin in drug-resistant tuberculosis.

Ziganshina, L. E. & Squire, S. B. Fluoroquinolones for treating tuberculosis. *Cochrane Database of Systematic Reviews* (2008).at <http://doi.wiley.com/10.1002/14651858.CD004795.pub3>

Background: Fluoroquinolones are sometimes used to treat multiple-drug-resistant and drug-sensitive tuberculosis. The effects of fluoroquinolones in tuberculosis regimens need to be assessed.

Objectives: To assess fluoroquinolones as additional or substitute components to antituberculous drug regimens for drug-sensitive and drug-resistant tuberculosis.

Search methods: In July 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2007, Issue 3), MEDLINE, EMBASE, LILACS, Science Citation Index, Database of Russian Publications, and metaRegister of Controlled Trials. We also scanned reference lists of all identified studies and contacted researchers.

Selection criteria: Randomized controlled trials of antituberculous regimens containing fluoroquinolones in people diagnosed with bacteriologically positive (sputum smear or culture) pulmonary tuberculosis.

Data collection and analysis: Two authors independently applied inclusion criteria, assessed the risk of bias in the trials, and extracted data. We used risk ratio (RR) for dichotomous data, mean difference (MD) for continuous data (both with 95% confidence intervals (CI)), and the random-effects model if we detected heterogeneity and it was appropriate to combine data.

Main results: Eleven trials (1514 participants) met the inclusion criteria. No statistically significant difference was found in trials substituting ciprofloxacin, ofloxacin or moxifloxacin for first-line drugs in relation to cure (416 participants, 3 trials), treatment failure (388 participants, 3 trials), or clinical or radiological improvement (216 participants, 2 trials). Substituting ciprofloxacin into first-line regimens in drug-sensitive tuberculosis led to a higher incidence of relapse (RR 7.17, 95% CI 1.33 to 38.58; 384 participants, 3 trials) and longer time to sputum culture conversion (MD 0.50 months, 95% CI 0.18 to 0.82; 168 participants, 1 trial), although this was confined to HIV-positive participants. Substituting for ethambutol in first-line regimens led to a higher incidence of total number of adverse events (RR 1.34, 95% CI 1.05 to 1.72; 492 participants, 2 trials). Adding or substituting levofloxacin to basic regimens in drug-resistant areas had no effect. A comparison of sparfloxacin versus ofloxacin added to regimens showed no statistically significant

difference in cure (184 participants, 2 trials), treatment failure (149 participants, 2 trials), or the total number of adverse events (253 participants, 3 trials).
Author's conclusions: Only ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin and moxifloxacin have been tested in randomized controlled trials for treating tuberculosis. We cannot recommend ciprofloxacin in treating tuberculosis. Trials of newer fluoroquinolones for treating tuberculosis are needed and are ongoing. No difference has been demonstrated between sparfloxacin and ofloxacin in drug-resistant tuberculosis.

Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Oregon Health Authority

Proton Pump Inhibitors (PPIs) and Histamine-2 Antagonists (H2As)

Month/Year of Review: November, 2012
PDL Class: Gastrointestinal- H2-Antagonists and PPI's
End date of literature search: November 12, 2012

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

Current Status of PDL Class:

- Preferred Agents:
  - *H2-Antagonists*: Cimetidine tablets, cimetidine HCL solution, famotidine tablets, ranitidine.
  - *PPI's*: Omeprazole capsules/tablets, pantoprazole tablets
- Non Preferred Agents:
  - *H2-Antagonists*: Nizatidine
  - *PPI's*: Lansoprazole, dexlansoprazole (Dexilant®), rabeprazole (Aciphex®), esomperazole (Nexium®), omeprazole/sodium bicarbonate (Zegrid®)

Previous Conclusions[1]**:**

H2-Angonists:

- Evidence does not support a difference in efficacy or harms
- Cimetidine has the most adverse events, ranitidine has the second most adverse events
- Consider inclusion of at least one agent from the H2-Antagonist class with special consideration for famotidine or ranitidine for pediatric use

PPIs:

- The evidence does not demonstrate a clinical difference in efficacy to justify selection of any PPI as clinically superior to the other drugs in the class.
- There are no clinically demonstrable differences amongst the PPIs whether treatment is for GERD, peptic ulcer, non-steroidal ulcer, duodenal ulcer, or eradication of Helicobacter Pylori.
- No evidence supports differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.

Current PA Criteria:

- Criteria in place for PPI's to promote PDL options, restrict chronic use to patients who failed H2-Antagonists, preferred PPIs or who have severe disease and restricts BID use to patients with severe disease, H.pylori or pediatric patients (Appendix A).

Conclusions:

- Patient should be re-evaluated for benefit and risk while being on long term PPI therapy for potential adverse events.
- No new evidence consistently supports a difference in efficacy or safety between agents.

Recommendation:

- No further review needed. Evaluate comparative costs in executive session.

Methods:

A MEDLINE Ovid search was conducted using proton pump inhibitors, H2-Angstonists, GERD, peptic ulcers and H.Pylori. The search was limited to meta-analysis, English language, and to studies conducted in humans since last DERP review in May 2009. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews (See Appendix B for Review Abstracts)

- In September 2011, the Agency for Healthcare Research and Quality published an update of its report "Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease.[4] The review found moderate strength of evidence that PPIs are superior to H2A's in the resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks. There was moderate strength of evidence demonstrating no significant differences between PPIs for relief of GERD symptoms at 4 weeks to 6 months. Based on 12 randomized controlled trials, there was moderate strength evidence that there were no consistent differences in doses and dosing regimens with different PPIs in relation to symptom resolution and esophagitis healing rates and no consistent difference in symptom relief and esophagitis healing rates between PPIs and over-the-counter dosage of PPIs approved for the treatment of frequent heartburn.

- There were two meta-analyses by Janarthanan S et al[5] and Deshpande et al[6] who investigated the association of Clostridium difficile-associated diarrhea (CDAD) and Clostridium difficile infection (CDI) with the use of PPIs respectively. The analysis done by Janarthanan reviewed of 23 studies including close to 300,000 patients who met the inclusion criteria. The results showed a 65% (summary risk estimate 1.69 with a 95% confidence interval (CI) from 1.395 to 1.974; P<0.000) increase in the incidence of CDAD among patients on PPIs. By study design, whether case–control study (17) or cohort study (6), there was still a significant increase in the incidence of CDAD among PPI users. The risk estimates were 2.31 (95% CI from 1.72 to 3.10; P<0.001) and 1.48 (95% CI from 1.25 to 1.75; P<0.001) for cohort and case–control studies, respectively. The authors concluded there was sufficient evidence to suggest that PPIs increase the incidence of CDAD. It was recommended by the authors that the routine use of PPIs for gastric ulcer prophylaxis should be more prudent and establishing a guideline for the use of PPI may help in the future with the judicious use of PPIs. This review used the Beff and Egger tests to evaluate the publication bias evaluation and the Duval and Tweedie "trim-and-fill" method for a sensitivity analysis. Deshphande et al. conducted a similar meta-analysis on plausible link between CDI and PPIs use. Two investigators screened articles independently for inclusion criteria, data extraction, and quality assessment; disagreements were resolved based on consensus with a third

investigator. Data were combined by means of a random-effects model and odds ratios were calculated. Subgroup and sensitivity analyses were performed based on study design and antibiotic use. The results from Thirty studies (25 case-control and 5 cohort) reported in 29 articles met the inclusion criteria (n = 202,965). PPI therapy increased the risk for CDI (odds ratio, 2.15, 95% confidence interval, 1.81–2.55), but there was significant heterogeneity in results among studies ($P < .00001$). This association remained after subgroup and sensitivity analyses, although significant heterogeneity persisted among studies. The authors also concluded PPI therapy was associated with a 2-fold increase in risk for CDI. Unlike Janarthanan S et al study, this analysis included observational studies that investigated the risk of CDI associated with PPI therapy and used CDI as an end point. Due to the observational nature of the analyzed studies, the authors were not able to study the causes of this association.

- In 2011 **Kwok et al**[7] conducted a meta-analysis on the risk of fractures with acid-suppressing medications. The review included 12 studies with total 1,521,062 patients. Pooled analysis of PPI use showed significant risk for spine fractures (4 studies, OR 1.50, 95% CI 1.32–1.72, $p < 0.001$, $I^2 = 0\%$) but this was not significant for H2RA (3 studies, OR 1.05, 95% CI 0.92–1.19, $p = 0.50$, $I^2 = 0\%$). Similarly for hip fractures, there was a significant risk of fractures with PPIs (10 studies, OR 1.23, 95% CI 1.11–1.36, $p < 0.001$, $I^2 = 72\%$), but not for H2RAs (9 studies, OR 1.12, 95% CI 0.99–1.27, $p = 0.06$, $I^2 = 75\%$), respectively). Analysis of fractures overall (based on all 12 studies covering a mixture of fracture types) yielded an OR of 1.20 (95% CI 1.11–1.30, $p < 0.001$, $I^2 = 78\%$) for PPIs, and OR of 1.08 (95% CI 1.00–1.18, $p = 0.06$, $I^2 = 82\%$) for H2RA. However, aside from the risk of spine fractures, all the other analyses were limited by substantial heterogeneity. One study that reported on a direct comparison between acid-suppressing medications found an increased risk with PPIs vs. H2RA for hip fractures, OR 1.34 (95% CI 1.14–1.38). The authors concluded some evidence for a modest association between PPI use and risk of fractures, which was not seen with H2RA exposure. The association is most consistent for spine fractures, while there is substantial heterogeneity in the magnitude of risk for other fractures. Clinicians who are concerned about patients with high fracture risk may wish to consider the option of H2RAs instead of PPIs. The authors performed random effects meta-analysis of odds ratios (OR) according to fracture type and conducted subgroup analyses by duration of exposure. Heterogeneity was assessed using the I^2 statistic.

- A 2011 **Cochrane review** by Rostom A et al[8] evaluated the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity. Randomized controlled clinical trials (RCTs) of prostaglandin analogues (PA), H2-receptor antagonists (H2RA) or proton pump inhibitors (PPI) for the prevention of chronic NSAID induced upper GI toxicity were included. Two independent authors extracted data regarding population characteristics, study design, methodological quality and number of participants with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs, drop outs due to symptoms. Heterogeneity was evaluated using a chi square test, and the I square statistic. Forty-one RCTs met the inclusion criteria. All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively, P=0.0055). A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhea at all doses, although significantly more at 800 ug/day than 400 ug/day (P=0.0012). Misoprostol also reduced the risk of clinical ulcer complications. Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40; 95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol. The authors concluded Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic

duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40; 95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.

- Another **Cochrane review** by Van Pinxteren et al[9] compared the efficacy of short term use of PPI, H2RA in adults with GERD, treated empirically and in those with endoscopy negative reflux disease. Randomised controlled trials reporting symptomatic outcome after short-term treatment for GERD using proton pump inhibitors, H2-receptor antagonists or prokinetic agents. Participants had to be either from an empirical treatment group (no endoscopy used in treatment allocation) or from an endoscopy negative reflux disease (ENRD) group (no signs of erosive esophagitis). Thirty-two trials (9738 participants) were included: fifteen in the empirical treatment group, thirteen in the ENRD group and four in both. In empirical treatment of GERD the relative risk (RR) for heartburn remission (the primary efficacy variable) in placebo-controlled trials for PPI was 0.37 (two trials, 95% confidence interval (CI) 0.32 to 0.44), for H2RAs 0.77 (two trials, 95% CI 0.60 to 0.99) and for prokinetics 0.86 (one trial, 95% CI 0.73 to 1.01). In a direct comparison PPIs were more effective than H2RAs (seven trials, RR 0.66, 95% CI 0.60 to 0.73) and prokinetics (two trials, RR 0.53, 95% CI 0.32 to 0.87). In treatment of ENRD, the RR for heartburn remission for PPI versus placebo was 0.73 (eight trials, 95% CI 0.67 to 0.78) and for H2RA versus placebo was 0.84 (two trials, 95% CI 0.74 to 0.95). The RR for PPI versus H2RA was 0.78 (three trials, 95% CI 0.62 to 0.97) and for PPI versus prokinetic 0.72 (one trial, 95% CI 0.56 to 0.92). The authors concluded PPIs are more effective than H2RAs in relieving heartburn in patients with GERD who are treated empirically and in those with ENRD, although the magnitude of benefit is greater for those treated empirically.

New Treatment Guidelines

National Institute for Health and Clinical Excellence (NICE) guideline on management of acute upper gastrointestinal bleeding[2] (June 2012)

Summary of Major Recommendations on PPIs and/or H2As (The type of evidence supporting the recommendations is not specifically stated):

- Do not offer acid-suppression drugs (proton pump inhibitors or H_2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding; offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent hemorrhage shown at endoscopy.
- Offer acid-suppression therapy (H_2-receptor antagonists or proton pump inhibitors) for primary prevention of upper gastrointestinal bleeding in acutely ill patients admitted to critical care. If possible, use the oral form of the drug; review the ongoing need for acid-suppression drugs for primary prevention of upper gastrointestinal bleeding in acutely ill patients when they recover or are discharged from critical care.

The 2012 treatment guidelines on GERD by University of Michigan Health System[3]

Summary of Major Recommendations on Pharmacologic Intervention: H2RAs, PPIs, and prokinetics have proven efficacy in the treatment of GERD *[I A]*. Prokinetics are as effective as H2RAs but are currently unavailable *[III A]*. Carafate and antacids are ineffective *[III A]*, but may be used as supplemental acid-neutralizing agents for certain patients with GERD *[II D]*.

- Non-erosive reflux disease (NERD): *Step-up* (H2RA then as followed by a PPI if no improvement) and *step-down* (PPI then followed by the lowest dose of acid suppression) therapy are equally effective for acute treatment and maintenance *[I B]*. *On demand* (patient-directed) therapy is the most cost-effective strategy *[I B]*.
- Erosive esophagitis: Initial PPI therapy is the treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis *[I A]*.
- Take PPI's 30-60 minutes prior to breakfast (and dinner if two times per day [BID]) to optimize effectiveness *[I B]*. Use generic and over-the-counter (OTC) formulations exclusively, eliminating need for prior authorizations.
- Patients should not be left on acid suppressive therapy without re-evaluation of symptoms to minimize cost and the potential adverse events from medications *[I B]*.

New drugs:
None

New indications:
June 2011: The indication for maintenance of healed erosive esophagitis for dexlansoprazole was expanded to include the relief of heartburn.

New FDA safety alerts:

Medication	Alert Date	FDA Alert
Clostridium difficile-associated diarrhea[10]	02/28/2012	PPIs may be associated with an increased risk of *Clostridium difficile*–associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve. FDA is also reviewing the risk of CDAD in users of H2-Antagonists.
Low magnesium level associated with long-term PPI use[11]	03/02/ 2011	Prescription PPIs may cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year). In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.
Avoid concomitant use of Plavix® and omeprazole[12]	10/27/2010	FDA issued a reminder that it **continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole** because the co-administration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature. Patients at risk of heart attacks or strokes, who are given Plavix to prevent blood clots, will not get the full anti-clotting effect if they also take omeprazole. Omeprazole is found in prescription products (Prilosec, Zegerid, and generic products) and over-the-counter products (Prilosec OTC, Zegerid OTC, and generic products).FDA wishes to emphasize additional facts that may be a source of confusion among healthcare professionals: • With regard to the proton pump inhibitor (PPI) drug class, this recommendation **applies only to omeprazole** and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP 2C19) that is crucial for conversion of Plavix into its active form.

		• Pantoprazole (Protonix) may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole.
Possible increased risk of fractures with the use of PPIs[13]	05/25/2010	Healthcare professionals and users of proton pump inhibitors should be aware of the possible increased risk of fractures of the hip, wrist, and spine with the use of prescription and over-the-counter PPIs, and weigh the known benefits against the potential risks when deciding to use them. The new safety information is based on FDA's review of several epidemiological studies that reported an increased risk of fractures of the hip, wrist, and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more (see Data Summary section).The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group. 03/23/2011 update: FDA has determined an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication "Drug Facts" label is not indicated at this time. Following a thorough review of available safety data, FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely. The available data show that patients at highest risk for fractures received high doses of prescription PPIs (higher than OTC PPI doses) and/or used a PPI for one year or more.

References:

1. McDonagh MS, Carson S, Thakurta S. Drug class review on proton pump inhibitors. *Update*. 2009. Available at: http://derp.ohsu.edu/final/PPI_%20final%20report_update%205_version%204_unshaded_09_May.pdf. Accessed November 12, 2012.

2. National Instutute for Health and Clinical Excellentce (NICE). National Guideline Clearinghouse | Acute upper gastrointestinal bleeding: management. 2012. Available at: zotero://attachment/1950/. Accessed November 12, 2012.

3. University of Michigan Health System. National Guideline Clearinghouse | Gastroesophageal reflux disease (GERD). 2012. Available at: http://www.guideline.gov/content.aspx?id=37564. Accessed November 12, 2012.

4. Ip SS, Chung MM, Moorthy DD, et al. *Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Update*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.

5. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am. J. Gastroenterol.* 2012;107(7):1001–1010.

6. Deshpande A, Pant C, Pasupuleti V, et al. Association Between Proton Pump Inhibitor Therapy and Clostridium difficile Infection in a Meta-Analysis. *Clinical Gastroenterology and Hepatology*. 2012;10(3):225–233.

7. Kwok CS, Yeong JK-Y, Loke YK. Meta-analysis: Risk of fractures with acid-suppressing medication. *Bone*. 2011;48(4):768–776.

8. Rostom A, Dube C, Wells GA, et al. Prevention of NSAID-induced gastroduodenal ulcers. In: The Cochrane Collaboration, Rostom A, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2002. Available at: http://summaries.cochrane.org/CD002296/medications-to-prevent-nsaid-induced-gastroduodenal-ulcers. Accessed November 12, 2012.

9. Van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. In: The Cochrane Collaboration, Numans ME, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010. Available at: http://summaries.cochrane.org/CD002095/short-term-treatment-with-medications-for-heartburn-symptoms. Accessed November 12, 2012.

10. Research C for DE and. Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm. Accessed November 9, 2012.

11. Research C for DE and. Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm. Accessed November 9, 2012.

12. Research C for DE and. Drug Safety and Availability - FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole. 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm231161.htm. Accessed November 9, 2012.

13. Corley DA, Kubo A, Zhao W, Quesenberry C. Proton Pump Inhibitors and Histamine-2 Receptor Antagonists Are Associated With Hip Fractures Among At-Risk Patients. *Gastroenterology*. 2010;139(1):93–101.

Appendix A

Proton Pump Inhibitors (PPIs)

Goal(s):

- Promote PDL options.
- Restrict chronic use (greater than eight weeks) to patients who failed H2-antagonist, preferred PPIs or who have severe disease, e.g. Barrett's, or Zollinger Ellison syndrome.
- Restrict BID use to patients with severe disease, H.pylori or pediatric patients.

Notes:

- This is a "global" PA.
- If an active PA for a PPI already exists, then any PPI will pay.
- A new PA is required if the dosing schedule changes, e.g., an active PA for once daily dosing restricts the PPI to once a day.
- BID dosing requires a new PA, however, the strength of the dose could be increased without an additional PA, e.g., a change from 20mg daily could be increased to 40 mg ONCE a day without an additional PA.

Length of Authorization: 2 weeks to lifetime (criteria specific)

Requires PA:

- Non-preferred drugs

Covered Alternatives

- Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml
- Individual components for treatment of H.pylori that are preferred products.

ROUTE	HICL	BRAND	GENERIC	FORMULATIONS
ORAL	021607	Nexium	esomeprazole	Capsules, delayed-release: 20, 40mg Suspension, delayed-release pkts: 10, 20, 40mg
ORAL	008993	Prevacid	lansoprazole	Capsules, delayed-release: 15, 30 mg Enteric coated granules for oral suspension, delayed release: 15, 30mg
ORAL	025742	Prevacid NapraPAC	lansoprazole + naproxen	Delayed release capsules + naproxen tablets kit - 15 – 375, 15 -500

ORAL	004673	Zegerid	omeprazole	Packet for solution: 20, 40mg Capsules: 20, 40mg
ORAL	36085	Kapdex	Dexlansoprazole	Capsules, delayed-release: 30, 60mg
ORAL	011590, 022008	Protonix	pantoprazole	Tablets, delayed-release: 20 mg, 40 mg Suspension, delayed-release: 40mg
ORAL	011590	pantoprazole	pantoprazole	Tablets, delayed-release: 20 mg, 40 mg
ORAL	018847	Aciphex	rabeprazole	Tablets, delayed-release: 20 mg

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD9 code	
2. Is drug requested preferred?	**Yes: Go to 4**	**No: Go to 3**
3. . Will the prescriber consider a change to a preferred product?	**Yes: Inform provider of covered alternatives in class.**	**No: Go to 4**
4. Is diagnosis a) Zollinger-Ellison (251.5)? b) Barrett's esophagus (530.85)? c) Multiple Endocrine Adenoma (237.4)? d) Malignant Mastoma (202.6)? e) MEN Type I (258.01)?	Yes: Approve for a life time; BID dosing OK.	No: Go to 5
5. Is the diagnosis dyspepsia (536.8)?	Yes: Pass to RPH, DENY (OHP coverage) Diagnosis is below the line; preferred agents are available without PA.	No: Go to 6
6. Has patient tried and failed Prilosec OTC 40mg/day for 8 week trial (2 weeks for H. Pylori)	Yes: Go to 7	No: Go to #12
7. Is diagnosis H.Pylori?	Yes: Approve for 2 weeks – BID dosing OK	No: Go to 8

8. Is diagnosis active GI bleed? (531.0-531.2, 532.0-532.2, 533.0-533.2, 534.0-534.2)	Yes: Approve for 8 weeks - BID dosing OK	No: Go to 9
9. Is diagnosis Gastric or Duodenal Ulcer (531.3-531.9, 531.3-532.9, 533.3-533.9, 534.3-534.9) and/or does patient have 2 or more of the following risk factors: - > 65 years - requires > 3 mths of NSAIDs, aspirin or steroids - on anticoagulation (warfarin, enoxapirin, etc.) - History of GI Bleed or Ulcer? -	Yes: Approve QD for 1 year, if previously failed an 8 week QD trial at highest dose approve BID for 1 year. May approve BID dosing for pediatrics <12 years old	No: Go to 10
10. Is the diagnosis symptomatic GERD (530.81, 530.10 – 530.19)	Yes: Approve QD dosing for 1 year; if previously failed an 8 week QD trial at highest dose approve BID for 1 year. May approve BID dosing for pediatrics<12 years old	No: Go to 11
11. Is diagnosis a) Ulcer of esophagus (530.2x) b) Stricture & stenosis of esophagus (530.3) c) Perforation of esophagus (530.4)	Yes: Approve up to BID for 1 year.	No: Go to 13
12. Is the request for Prevacid Solutab or Zegerid for tube administration?	Yes: Approve QD dosing for 1 year. May approve BID dosing for pediatrics <12 years old.	No: Pass to RPH. Deny and recommend omeprazole 20 mg QD or BID.
13. All other diagnoses will need to be evaluated by a pharmacist for appropriateness and OHP line coverage.	• Diagnoses above the line and where PPI is appropriate can be covered. • Diagnoses below the line and where PPI is appropriate should be denied as not covered. • Diagnoses above the line but where PPIs are not appropriate should be denied and not medically appropriate.	

Appendix B:

Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Sep. Report No.: 11-EHC049-EF.AHRQ Comparative Effectiveness Reviews.

BACKGROUND:Gastroesophageal reflux disease (GERD) is one of the most common health conditions affecting Americans. Despite the availability of medical, surgical, and endoscopic options, optimal management strategies remain unsettled.

PURPOSE:The purpose was to systematically review and update our previous Comparative Effectiveness Review, which compared the effectiveness of different management options for adults with GERD.

DATA SOURCES:We searched MEDLINE,® Cochrane Central Register of Controlled Trials, and other relevant databases, as well as other existing systematic reviews.

STUDY SELECTION:Studies of various designs were sought, including comparative randomized controlled trials, nonrandomized and cohort studies, and systematic reviews.

DATA EXTRACTION:A standardized protocol was used to extract details on study design, diagnoses, interventions, outcomes, and quality.

DATA SYNTHESIS:In total, 166 studies met eligibility criteria. We found a moderate strength of evidence that laparoscopic fundoplication in patients whose GERD symptoms were already well controlled by medical treatments was at least as effective as continued medical treatment (and in some cases superior) in controlling GERD-related symptoms for the first 1 to 3 years following surgery. However, the rate of serious adverse events was generally higher in patients who underwent fundoplication compared with those who had medical treatment. We did not identify sufficient evidence to conclude whether medical or surgical treatment was more effective in preventing long-term complications of GERD, such as the development of Barrett's esophagus or esophageal adenocarcinoma. We found a moderate strength of evidence that proton pump inhibitors were superior to histamine-2 receptor antagonists in resolving GERD symptoms at 4 weeks and promoting healing of esophagitis at 8 weeks. Evidence regarding the effectiveness of endoscopic procedures was insufficient. Evidence regarding the effectiveness of treatment of GERD on asthma symptoms was inconclusive.

LIMITATIONS:Studies directly comparing surgery to medical therapy generally had high dropout rates in long-term followup. There was a great deal of variability in the rigor with which the outcomes were evaluated across studies, particularly in subjective endpoints.

CONCLUSIONS:Medical therapy and laparoscopic fundoplication were similarly effective in improving GERD symptoms in patients whose symptoms were already well controlled by medical therapy for at least the first 1 to 3 years following surgery. Serious adverse events were more common after surgery. The effectiveness of endoscopic procedures remains substantially uncertain.

Clostridium difficile-Associated Diarrhea and Proton Pump Inhibitor Therapy: A Meta-Analysis

Sailajah Janarthanan, Ivo Ditah, Douglas G Adler and Murray N Ehrinpreis. *The American Journal of Gastroenterology* **107**, 1001-1010 (July 2012) | doi:10.1038/ajg.2012.179

Abstract

Objectives: Clostridium difficile-associated diarrhea (CDAD) is a major cause of morbidity and increasing health-care costs among hospitalized patients. Although exposure to antibiotics remains the most documented risk factor for CDAD, attention has recently been directed toward a plausible link with proton pump inhibitors (PPIs). However, the results of studies on the association between CDAD and PPIs remain controversial. We have conducted a meta-analysis to summarize the association between PPIs and CDAD among hospitalized patients.

Methods: A systematic search of published literature on studies that investigated the association between PPIs and CDAD from 1990 to 2010 was conducted on Medline and PubMed. The identified articles were reviewed for additional references. The most adjusted risk estimates were extracted by two authors and summarized using random effects meta-analysis. We also conducted a subgroup analysis by study design. Publication bias was evaluated using the Begg and Egger tests. A sensitivity analysis using the Duval and Tweedie "trim-and-fill" method has also been performed.

Results: Twenty-three studies including close to 300,000 patients met the inclusion criteria. There was a 65% (summary risk estimate 1.69 with a 95% confidence interval (CI) from 1.395 to 1.974; P<0.000) increase in the incidence of CDAD among patients on PPIs. By study design, whether case–control study (17) or cohort study (6), there was still a significant increase in the incidence of CDAD among PPI users. The risk estimates were 2.31 (95% CI from 1.72 to 3.10; P<0.001) and 1.48 (95% CI from 1.25 to 1.75; P<0.001) for cohort and case–control studies, respectively.

Conclusions: There is sufficient evidence to suggest that PPIs increase the incidence of CDAD. Our meta-analysis shows a 65% increase in the incidence of CDAD among PPI users. We recommend that the routine use of PPIs for gastric ulcer prophylaxis should be more prudent. Establishing a guideline for the use of PPI may help in the future with the judicious use of PPIs. Further studies, preferably prospective, are needed to fully explore the association between PPIs and CDAD.

Association Between Proton Pump Inhibitor Therapy and *Clostridium difficile* Infection in a Meta-Analysis

Abhishek Deshpande, Chaitanya Pant, Vinay Pasupuleti, David D.K. Rolston, Anil Jain, Narayan Deshpande, Priyaleela Thota, Thomas J. Sferra, Adrian V. Hernandez. *Clinical Gastroenterology and Hepatology.* Volume 10, Issue 3, March 2012, Pages 225–233

Background & Aims: In the past decade, there has been a growing epidemic of *Clostridium difficile* infection (CDI). During this time, use of proton pump inhibitors (PPIs) has increased exponentially. We evaluated the association between PPI therapy and the risk of CDI by performing a meta-analysis.

Methods: We searched MEDLINE and 4 other databases for subject headings and text words related to CDI and PPI in articles published from 1990 to 2010. All observational studies that investigated the risk of CDI associated with PPI therapy and used CDI as an end point were considered eligible. Two investigators screened articles independently for inclusion criteria, data extraction, and quality assessment; disagreements were resolved based on consensus with a third investigator. Data were combined by means of a random-effects model and odds ratios were calculated. Subgroup and sensitivity analyses were performed based on study design and antibiotic use.

Results: Thirty studies (25 case-control and 5 cohort) reported in 29 articles met the inclusion criteria (n = 202,965). PPI therapy increased the risk for CDI (odds ratio, 2.15, 95% confidence interval, 1.81–2.55), but there was significant heterogeneity in results among studies (P < .00001). This association remained after subgroup and sensitivity analyses, although significant heterogeneity persisted among studies.

Conclusions: PPI therapy is associated with a 2-fold increase in risk for CDI. Because of the observational nature of the analyzed studies, we were not able to study the causes of this association. Further studies are needed to determine the mechanisms by which PPI therapy might increase risk for CDI.

Meta-analysis: Risk of fractures with acid-suppressing medication.

Chun Shing Kwok, Jessica Ka-Yan Yeong, Yoon Kong Loke School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ, UK. *Bone* Volume 48, Issue 4, 1 April 2011, Pages 768–776

Abstract

Aims: Recent studies have suggested an increased risk of fractures with proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). We planned to perform a meta-analysis of fractures in patients taking PPIs and H2RAs.

Methods: We searched MEDLINE and EMBASE in September 2010 for observational studies reporting on the risk of fractures with acid-suppressing medication (PPIs and H2RA). We also checked the references lists of included studies and regulatory authority websites for additional data. We performed random effects meta-analysis of odds ratios (OR) according to fracture type and conducted subgroup analyses by duration of exposure. Heterogeneity was assessed using the I^2 statistic.

Results: Our review included 12 studies covering 1,521,062 patients. Pooled analysis of PPI use showed significant risk for spine fractures (4 studies, OR 1.50, 95% CI 1.32–1.72, $p < 0.001$, $I^2 = 0\%$) but this was not significant for H2RA (3 studies, OR 1.05, 95% CI 0.92–1.19, $p = 0.50$, $I^2 = 0\%$). Similarly for hip fractures, there was a significant risk of fractures with PPIs (10 studies, OR 1.23, 95% CI 1.11–1.36, $p < 0.001$, $I^2 = 72\%$), but not for H2RAs (9 studies, OR 1.12, 95% CI 0.99–1.27, $p = 0.06$, $I^2 = 75\%$), respectively). Analysis of fractures overall (based on all 12 studies covering a mixture of fracture types) yielded an OR of 1.20 (95% CI 1.11–1.30, $p < 0.001$, $I^2 = 78\%$) for PPIs, and OR of 1.08 (95% CI 1.00–1.18, $p = 0.06$, $I^2 = 82\%$) for H2RA. However, aside from the risk of spine fractures, all the other analyses were limited by substantial heterogeneity. One study that reported on a direct comparison between acid-suppressing medications found an increased risk with PPIs vs. H2RA for hip fractures, OR 1.34 (95% CI 1.14–1.38).

Conclusion: There is some evidence for a modest association between PPI use and risk of fractures, which was not seen with H2RA exposure. The association is most consistent for spine fractures, while there is substantial heterogeneity in the magnitude of risk for other fractures. Clinicians who are concerned about patients with high fracture risk may wish to consider the option of H2RAs instead of PPIs.

Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD002296. DOI: 10.1002/14651858.CD002296.

Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are among the most frequently prescribed medications in North America and Europe. However, there is overwhelming evidence linking these agents to a variety of gastrointestinal (GI) toxicities.

Objectives: To review the effectiveness of common interventions for the prevention of NSAID induced upper GI toxicity.

Search methods: We searched MEDLINE from 1966 to May 2009, Current Contents for six months prior to May 2009, EMBASE to May 2009, and the Cochrane Controlled Trials Register from 1973 to May 2009. Recent conference proceedings were reviewed and content experts and companies were contacted.

Selection criteria: Randomized controlled clinical trials (RCTs) of prostaglandin analogues (PA), H2-receptor antagonists (H2RA) or proton pump inhibitors (PPI) for the prevention of chronic NSAID induced upper GI toxicity were included.

Data collection and analysis: Two independent authors extracted data regarding population characteristics, study design, methodological quality and number of participants with endoscopic ulcers, ulcer complications, symptoms, overall drop-outs, drop outs due to symptoms. Dichotomous data were pooled using RevMan 5.0. Heterogeneity was evaluated using a chi square test, and the I square statistic.

Main results: Forty-one RCTs met the inclusion criteria. All doses of misoprostol significantly reduced the risk of endoscopic ulcers. Misoprostol 800 ug/day was superior to 400 ug/day for the prevention of endoscopic gastric ulcers (RR 0.17, and RR 0.39 respectively, P=0.0055). A dose response relationship was not seen with duodenal ulcers. Misoprostol caused diarrhea at all doses, although significantly more at 800 ug/day than 400 ug/day (P=0.0012). Misoprostol also reduced the risk of clinical ulcer complications. Standard doses of H2RAs were effective at reducing the risk of endoscopic duodenal (RR 0.36; 95% CI 0.18 to 0.74) but not gastric ulcers (RR 0.73; 95% CI 0.50 to 1.08). Both double dose H2RAs and PPIs were effective at reducing the risk of endoscopic duodenal and gastric ulcers (RR 0.44; 95% CI 0.26 to 0.74) and RR=0.40;95% CI; 0.32-0.51 respectively for gastric ulcer), and were better tolerated than misoprostol.

Authors' conclusions: Misoprostol, PPIs, and double dose H2RAs are effective at preventing chronic NSAID related endoscopic gastric and duodenal ulcers. Lower doses of misoprostol are less effective and are still associated with diarrhea. In patients with previous NSAID bleeds, a COX-2 inhibitor alone is equivalent to a NSAID+PPI, though the re-bleeding rates with both strategies are still relatively high. A strategy of a COX-2 inhibitor+PPI appears to offer the greatest GI safety in high risk patients.

Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-esophageal reflux disease-like symptoms and endoscopy negative reflux disease

Bart van Pinxteren, Kirsten E Sigterman,Peter Bonis, Joseph Lau, Mattijs E Numans. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD002095. DOI: 10.1002/14651858.CD002095.pub4.

Abstract

Background: Approximately 25% of adults regularly experience heartburn, a symptom of gastro-oesophageal reflux disease (GORD). Most patients are treated empirically (without specific diagnostic evaluation e.g. endoscopy. Among patients who have an upper endoscopy, findings range from a normal appearance, mild erythema to severe oesophagitis with stricture formation. Patients without visible damage to the esophagus have endoscopy negative reflux disease (ENRD). The pathogenesis of ENRD, and its response to treatment may differ from GORD with oesophagitis.

Objectives: Summarise, quantify and compare the efficacy of short-term use of proton pump inhibitors (PPI), H2-receptor antagonists (H2RA) and prokinetics in adults with GORD, treated empirically and in those with endoscopy negative reflux disease (ENRD).

Search methods: We searched MEDLINE (January 1966 to November 2008), EMBASE (January 1988 to November 2008), and EBMR in November 2008.

Selection criteria: Randomized controlled trials reporting symptomatic outcome after short-term treatment for GORD using proton pump inhibitors, H2-receptor antagonists or prokinetic agents. Participants had to be either from an empirical treatment group (no endoscopy used in treatment allocation) or from an endoscopy negative reflux disease group (no signs of erosive oesophagitis).

Data collection and analysis: Two authors independently assessed trial quality and extracted data.

Main results: Thirty-two trials (9738 participants) were included: fifteen in the empirical treatment group, thirteen in the ENRD group and four in both. In empirical treatment of GORD the relative risk (RR) for heartburn remission (the primary efficacy variable) in placebo-controlled trials for PPI was 0.37 (two trials, 95% confidence interval (CI) 0.32 to 0.44), for H2RAs 0.77 (two trials, 95% CI 0.60 to 0.99) and for prokinetics 0.86 (one trial, 95% CI 0.73 to 1.01). In a direct comparison PPIs were more effective than H2RAs (seven trials, RR 0.66, 95% CI 0.60 to 0.73) and prokinetics (two trials, RR 0.53, 95% CI 0.32 to 0.87). In treatment of ENRD, the RR for heartburn remission for PPI versus placebo was 0.73 (eight trials, 95% CI 0.67 to 0.78) and for H2RA versus placebo was 0.84 (two trials, 95% CI 0.74 to 0.95). The RR for PPI versus H2RA was 0.78 (three trials, 95% CI 0.62 to 0.97) and for PPI versus prokinetic 0.72 (one trial, 95% CI 0.56 to 0.92).

Authors' conclusions: PPIs are more effective than H2RAs in relieving heartburn in patients with GORD who are treated empirically and in those with ENRD, although the magnitude of benefit is greater for those treated empirically.

Drug Class Review

Newer Antihistamines

Preliminary Scan Report 1
Update 3

November 2012

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the US Food and Drug Administration since the last report. Other important studies could exist.

Date of Last Update Report

Update 2, May 2010 (searches through December 2009)

Date of Last Preliminary Update Scan Report

None since most recent update report

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The Participating Organizations of Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

> Key question 1. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?
>
> Key question 2. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in harms?
>
> Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), co-morbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer harms?

Inclusion Criteria

Populations

- Adult or pediatric outpatients with the following conditions:

  - Seasonal allergic rhinitis
  - Perennial allergic rhinitis
  - Urticaria (acute and chronic)
- Subgroups of interest included, but were not limited to, different races, ages (older adult compared with younger adult), concomitant use of other medications (in consideration of drug-drug interactions), persons with various comorbidities (pregnancy and consideration of drug-disease interactions), and sex.

Interventions

Table 1. Included drugs and their labeled indications

Drug	Trade name(s)	Labeled indications	Dosage form/Route
Cetirizine hydrochloride	Zyrtec®	SAR; PAR; Chronic Urticaria	Syrup/Oral
	Reactine®[a]	SAR[b]; PAR; Chronic Urticaria[c]	Tablet; Chewable tablet; Syrup/Oral
Loratadine	Claritin®	SAR; PAR[a]; Chronic Urticaria	Tablet; ODT[a]; Syrup; Capsule[d]/Oral
Fexofenadine hydrochloride	Allegra®	SAR; PAR[a]; Chronic Urticaria	Tablet; ODT; Suspension; Capsule[a] /Oral
Desloratadine	Clarinex®[d]	SAR; PAR; Chronic Urticaria	Tablet; ODT; Syrup/ Oral
	Aerius®[a]	Allergic Rhinitis[c]; SAR[b]; Chronic Urticaria	Tablet; Syrup/Oral
Levocetirizine	Xyzal®[d]	SAR; PAR; Chronic Urticaria	Tablet; Solution/Oral
Azelastine	Astelin®[d]	SAR	Spray; Metered/Nasal
	Astepro®[d]	SAR; PAR	Spray; Metered/Nasal
Olopatadine	Patanase®[d]	SAR	Spray; Metered/Nasal

Abbreviations: ODT, orally disintegrating tablet; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.
[a] Only available in Canada.
[b] For children only.
[c] For adults only.
[d] Not available in Canada.

Study designs

1. Efficacy and effectiveness
    a. Randomized controlled trials, controlled clinical trials, and systematic reviews of fair or better quality.
    b. Direct comparisons (head-to-head studies) were preferred over indirect comparisons using active or placebo-controlled trials. Inclusion of indirect evidence will be considered where there is insufficient direct evidence.
    c. Studies ≥1 week in duration were included.
    d. Studies conducted in artificial study settings (for example, antigen exposure chambers) were not be included. Abstracts and conference proceedings are also excluded.

2. Harms
    a. Randomized controlled trials, controlled clinical trials, pre-compared with post-design studies, and observational studies with comparative groups.
    b. To be included, reports about overall harms or adverse events had to report total withdrawals, withdrawals due to specific adverse events (for example, central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention, etc.), or the frequency and severity of these specific adverse events.

Outcomes

The following were the primary outcomes for this review:

- Efficacy and effectiveness
    - Symptoms (nasal congestion, rhinorrhea, sneezing, itching and pain from skin irritations)
    - Functional capacity (physical, social and occupational functioning, quality of life)
    - Time to relief of symptoms (time to onset, duration of relief)
    - Duration of effectiveness (switch rate)
- Harms
    - Total withdrawals
    - Withdrawals due to adverse events
    - Serious adverse events or withdrawals due to specific adverse events (central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention)

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from December 2009 through November 2012 using terms for included drugs. We also searched the US Food and Drug Administration website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan
None.

New drugs identified in previous Preliminary Update Scan(s)
No scan since most recent update report.

New Indications

New indications identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scan(s)
No scan since most recent update report.

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
We identified a protocol of a potentially relevant comparative effectiveness review produced by the Agency for Healthcare Research and Quality Effective Health Care Program. See appendix A for the key questions that describe the scope of the project.

Treatments for Seasonal Allergic Rhinitis, published online March 8, 2012
http://effectivehealthcare.ahrq.gov/ehc/products/376/1000/SAR_Protocol_20120308.pdf

Reviews identified in previous Preliminary Update Scan(s) <if relevant>
No other scans since most recent update report.

Randomized Controlled Trials

Trials identified since the most recent Full Report
Medline searches resulted in 81 citations. Of those, there are 5 new potentially relevant head to head trials (see Appendix B for abstracts). Four out of 5 trials have levocetirizine as a treatment arm while 3 out of 5 trials have desloratadine as a treatment arm. There are three trials on allergic rhinitis and 2 on urticaria. Table 1 summarizes the populations and comparisons included in these studies. Titles and abstracts for these citations are also available in appendix B. Additionally, there are 19 new placebo controlled trials identified in this scan most of which pertain to comparisons of levoceterizine and olopatadine to placebo. These trials would not be included in a Drug Effectiveness Review Project update if we were to create streamlined reports focusing on head to head trials only.

Table 2. Characteristics of new head-to-head trials

Study	N, Duration	Population	Comparison	Focus
Ciebiada, 2011	40, 32 weeks	Adults with allergic rhinitis	Montelukast, levocetirizine, desloratadine, montelukast+levocetirizine, montelukast+desloratadine	Symptom relief and score
LaForce, 2010	NR, 14 days	Patients ≥12 years of age with seasonal allergic rhinitis	Olopatadine nasal spray 0.6%+fluticasone nasal spray, Azelastine nasal spray 0.1%+fluticasone nasal spray	Symptom relief and scores, harms
Tzanetos, 2011	30, 3 months	Patients with perennial allergic rhinitis	Cetirizine 5 mg, Levocetirizine 5mg	Sedation
Hong, 2010 (no abstract)	NR	Chronic idiopathic urticaria	Desloratadine 5 mg, Levocetirizine 5 mg	NR
Staevska, 2010	80, NR	Adults with urticaria	Desloratadine max dose 20 mg, Levocetirizine max dose 20 mg	Symptom relief and scores, harms

New Safety Alerts

Identified in this Preliminary Update Scan

Patanase® (olopatadine hydrochloride) nasal spray: ***as of February 2012,*** the following labeling revision

WARNINGS AND PRECAUTIONS

Nasal Septal Perforation:

- In the third safety trial, 1 patient exposed to the 3.7 pH vehicle nasal spray (containing no povidone) reported a nasal septal perforation.

Xyzal® (levocetirizine dihydrochloride) oral solution and tablets: as of September 2012, the following labeling revision

WARNINGS AND PRECAUTIONS

Urinary Retention

Urinary retention has been reported post-marketing.

Identified in previous Preliminary Update Scan(s)

No scan since most recent update report.

Summary and Recommendations

There are no new drugs and no new indications available for the newer antihistamines. Bilastine and Rupatadine are yet to receive US Food and Drug Administration approval. The volume and

nature of the head to head trials is not very compelling. The Evidence-based Practice Center is not recommending a new update or a summary review or an addendum at this time.

Appendix A. Systematic review produced by the Effective Health Care Program

Treatments for Seasonal Allergic Rhinitis

The Key Questions

Question 1

What is the comparative effectiveness of pharmacologic treatments, alone or in combination with each other, for adults and adolescents (≥12 years of age) with mild or with moderate/severe seasonal allergic rhinitis (SAR)?

1. How does effectiveness vary with long-term (months) or short-term (weeks) use?
2. How does effectiveness vary with intermittent or continuous use?
3. For those with symptoms of allergic conjunctivitis, does pharmacologic treatment of SAR provide relief of eye symptoms (itching, tearing)?
4. For those codiagnosed with asthma, does pharmacologic treatment of SAR provide asthma symptom relief?

Question 2

What are the comparative adverse effects of pharmacologic treatments for SAR for adults and adolescents (≥12 years of age)?

1. How do adverse effects vary with long-term (months) and short-term (weeks) use?
2. How do adverse effects vary with intermittent or continuous use?

Question 3

For the subpopulation of pregnant women, what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

1. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
2. How do effectiveness and adverse effects vary with intermittent or continuous use?

Question 4

For the subpopulation of children (<12 years of age), what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

1. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
2. How do effectiveness and adverse effects vary with intermittent or continuous use?

Appendix B. Abstracts of potentially relevant new trials of Newer Antihistamines

Ciebiada, M., M. Gorska-Ciebiada, et al. (2011). "Use of montelukast alone or in combination with desloratadine or levocetirizine in patients with persistent allergic rhinitis." American Journal of Rhinology & Allergy **25**(1): e1-6.

BACKGROUND: We assessed the course of treatment in patients with persistent allergic rhinitis (AR) treated with montelukast, levocetirizine, or desloratadine alone or combinations of antihistamine and montelukast. METHODS: A 32-week randomized, double-blind, placebo-controlled, crossover, double-armed study in 40 adult patients with history of persistent AR, clinical allergy to house-dust mites, and a total nasal symptom score of at least 5 (congestion of at least 2) has been performed. Patients with asthma, chronic obstructive pulmonary disease, nonallergic rhinitis with clinical allergy associated with seasonal allergens, and other serious diseases were excluded. There were four 6-week treatment periods separated by 2-week washout periods. Twenty patients received either montelukast or antihistamine, a combination of montelukast and antihistamine, or placebo. The sequence of treatment was randomly assigned. Nasal symptoms were assessed using a 4-point scale at baseline, daily during the 1st week and on days 14, 21, 28, 35, and 42 of treatment. RESULTS: Montelukast alone, levocetirizine alone, desloratadine alone, and the montelukast/antihistamine combinations significantly improved nasal symptoms during the first 24 hours. Improvement gradually increased during the 6 weeks of treatment, especially in patients receiving montelukast alone or in combination therapy with the antihistamine in both arms. Improvement at 42 days of treatment was significantly greater than that achieved on the 1st day of therapy in patients treated with the combination of montelukast and levocetirizine. CONCLUSION: Montelukast alone or in combination with antihistamines gave a gradual increase in nasal symptom improvement within 6 weeks of treatment in patients with persistent AR.

Hong, J.-B., H.-C. Lee, et al. (2010). "A randomized, double-blind, active-controlled, parallel-group pilot study to compare the efficacy and sedative effects of desloratadine 5 mg with levocetirizine 5 mg in the treatment of chronic idiopathic urticaria." Journal of the American Academy of Dermatology **63**(5): e100-102.

LaForce, C. F., W. Carr, et al. (2010). "Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis." Allergy & Asthma Proceedings **31**(2): 132-140.

The combination of intranasal antihistamines and intranasal corticosteroids results in superior relief of seasonal allergic rhinitis (SAR) symptoms compared with monotherapy. This study was designed to evaluate the safety and efficacy of olopatadine hydrochloride nasal spray, 0.6% (OLO), administered in combination with fluticasone nasal spray, 50 micrograms (FNS), relative to azelastine nasal spray, 0.1% (AZE), administered in combination with FNS in the treatment of

SAR. This was a multicenter, double-blind, randomized, parallel-group comparison of OLO + FNS versus AZE + FNS administered for 14 days to patients > or =12 years of age with histories of SAR. Efficacy assessments recorded by patients in a daily diary included nasal symptom scores. Safety was evaluated based on adverse events (AEs). Pretreatment values for reflective total nasal symptoms scores (rTNSS) were similar for both treatment groups. The mean (SD) 2-week average rTNSS was 4.28 (2.63) for OLO + FNS and 4.15 (2.63) for AZE + FNS; these scores were not statistically different between treatment groups. No significant differences ($p > 0.05$) between OLO + FNS and AZE + FNS were observed for the average 2-week percent changes from baseline in rTNSS or in the individual nasal symptoms (nasal congestion, rhinorrhea, itchy nose, and sneezing). Compared with baseline, both groups had statistically significant improvement in rTNSS ($p < 0.05$). No serious AEs were reported in either group during the study period. Overall, 19 AEs were reported in the OLO + FNS group and 29 AEs were reported in the AZE + FNS group. OLO, when administered adjunctively with FNS, is effective, safe, and well-tolerated in patients with SAR.

Staevska, M., T. A. Popov, et al. (2010). "The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria." Journal of Allergy & Clinical Immunology **125**(3): 676-682.

BACKGROUND: H(1)-antihistamines are first line treatment of chronic urticaria, but many patients do not get satisfactory relief with recommended doses. European guidelines recommend increased antihistamine doses of up to 4-fold. OBJECTIVE: To provide supportive evidence for the European guidelines. METHODS: Eighty tertiary referral patients with chronic urticaria (age range, 19-67 years) were randomized for double-blind treatment with levocetirizine or desloratadine (40/40). Treatment started at the conventional daily dose of 5 mg and then increased weekly to 10 mg, 20 mg, or 20 mg of the opposite drug if relief of symptoms was incomplete. Wheal and pruritus scores, quality of life, patient discomfort, somnolence, and safety were assessed. RESULTS: Thirteen patients became symptom-free at 5 mg (9 levocetirizine vs 4 desloratadine), compared with 28 subjects on the higher doses of 10 mg (8/7) and 20 mg (5/1). Of the 28 patients nonresponsive to 20 mg desloratadine, 7 became symptom-free with 20 mg levocetirizine. None of the 18 levocetirizine nonresponders benefited with 20 mg desloratadine. Increasing antihistamine doses improved quality of life but did not increase somnolence. Analysis of the effect of treatment on discomfort caused by urticaria showed great individual heterogeneity of antihistamine responsiveness: approximately 15% of patients were good responders, approximately 10% were nonresponders, and approximately 75% were responders to higher than conventional antihistamine doses. No serious or severe adverse effects warranting discontinuation of treatment occurred with either drug. CONCLUSION: Increasing the dosage of levocetirizine and desloratadine up to 4-fold improves chronic urticaria symptoms without compromising safety in approximately three quarters of patients with difficult-to-treat chronic urticaria.

Tzanetos, D. B., J. M. Fahrenholz, et al. (2011). "Comparison of the sedating effects of levocetirizine and cetirizine: a randomized, double-blind, placebo-controlled trial." Annals of Allergy, Asthma, & Immunology **107**(6): 517-522.

BACKGROUND: Compared with placebo, levocetirizine has been found to be less sedating than cetirizine in separate trials. However, whether levocetirizine is less sedating than its parent drug cetirizine has not yet been studied in a randomized trial. OBJECTIVE: To determine whether levocetirizine is less sedating than cetirizine. METHODS: We conducted a randomized, double-blind, crossover, placebo-controlled trial examining sedation and allergy symptoms in patients with perennial allergic rhinitis who had previously reported significant sedation with cetirizine. Enrollment ran from January 28, 2009, to February 25, 2009. All patients completed the study by April 17, 2009. Thirty patients enrolled, and 29 patients completed the study (1 patient did not return her questionnaire). In a double-blind fashion, the 29 study participants received levocetirizine, 5 mg daily for 1 week, cetirizine, 10 mg daily for 1 week, and an equivalent placebo pill for 1 week in randomized order with washout periods before each treatment arm. At the end of each washout period and each treatment period, participants completed a 1-page questionnaire. This questionnaire included questions about sedation or sleepiness in the form of a modified Epworth Sleepiness Scale, a Likert scale measuring general or global sedation, and allergy symptoms as measured by the total rhinitis symptom score. RESULTS: Sedation as measured by both the modified Epworth Sleepiness Scale and the Likert scale was not significantly different between the levocetirizine and cetirizine treatments. CONCLUSIONS: In patients with a perceived history of sedation with cetirizine, most were able to tolerate levocetirizine. However, this controlled trial also suggests that many of these patients would tolerate cetirizine if given in a masked manner. Therefore, patients with a history of mild to moderate sedation with cetirizine are unlikely to experience a different sedation profile with levocetirizine. Copyright Copyright 2011 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.