Drug Utilization Review Board

Oklahoma Health Care Authority
2401 N.W. 23rd Street, Suite 1A
Oklahoma City, Oklahoma 73107
Ponca Room

Wednesday
May 11, 2011
6:00 p.m.

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Shellie Keast, Pharm.D., M.S.

SUBJECT: Packet Contents for Board Meeting – May 11, 2011

DATE: May 5, 2011

NOTE: THE DUR BOARD WILL MEET AT 6:00 P.M. THE MEETING WILL BE HELD IN THE PONCA ROOM AT THE OKLAHOMA HEALTH CARE AUTHORITY OFFICES IN SHEPHERD MALL. (NORTH ENTRANCE)

Enclosed are the following items related to the May meeting. Material is arranged in order of the Agenda.

Call to Order

Public Comment Forum

Action Item – Approval of DUR Board Meeting Minutes – See Appendix A.

Update on DUR / MCAU Program – See Appendix B.

Action Item – Vote to Prior Authorize Pradaxa®– See Appendix C.

Action Item –Vote to Prior Authorize Dulera® and Update Criteria – See Appendix D.

Action Item – Vote to Prior Authorize Sumavel® and Update Anti-Migraine PBPA Criteria – See Appendix E.

Action Item – Annual Review of Anti-Ulcer Medications and Vote to Update Prior Authorization Criteria – See Appendix F.

Action Item – Vote to Update ADHD/Narcolepsy Prior Authorization Criteria – See Appendix G.

30 Day Notice to Prior Authorize Topical Corticosteroids® – See Appendix H.

Questions Regarding Posted 30 Day Notices – See Appendix I.

FDA and DEA Updates – See Appendix J.

Future Business

Adjournment

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Oklahoma Health Care Authority
Drug Utilization Review Board
(DUR Board)
Meeting – May 11, 2011 @ 6:00 p.m.

Oklahoma Health Care Authority
2401 N.W. 23rd Street, Suite 1-A
Oklahoma City, Oklahoma 73107
Ponca Room (North Entrance)

AGENDA
Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. Call To Order
- A. Roll Call – Dr. Graham

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum
- A. Acknowledgment of Speakers and Agenda Items

Items to be presented by Dr. Muchmore, Chairman:

3. Action Item – Approval of DUR Board Meeting Minutes – See Appendix A.
- A. April 13, 2011 DUR Minutes – Vote
- B. April 14, 2011 DUR Recommendation Memorandum

Items to be presented by Dr. Keast, Dr. Muchmore, Chairman:

4. Update on DUR / Medication Coverage Authorization Unit – See Appendix B.
- A. Retrospective Drug Utilization Review for March 2011
- B. Retrospective Drug Utilization Review Response for December 2010
- C. Medication Coverage Activity Audit for April 2011
- D. Pharmacy Help Desk Activity Audit for April 2011

Items to be presented by Dr. Keast, Dr. Muchmore, Chairman

5. Action Item – Vote to Prior Authorize Pradaxa® – See Appendix C.
- A. COP Recommendations

Items to be presented by Dr. Le, Dr. Muchmore, Chairman

6. Action Item – Vote to Prior Authorize Dulera® and Update Criteria – See Appendix D.
- A. Utilization Review of Long Acting Beta Agonists
- B. COP Recommendations

Items to be presented by Dr. Sipols, Dr. Muchmore, Chairman

7. Action Item – Vote to Prior Authorize Sumavel® and Update Anti-Migraine PBPA Criteria – See Appendix E.

A. Current Authorization Criteria
B. COP Recommendations

Items to be presented by Dr. Moore, Dr. Muchmore, Chairman

8. Action Item – Annual Review of Anti-Ulcer Medications and Vote to Update Prior Authorization Criteria – See Appendix F.

A. Current Authorization Criteria
B. Utilization Review
C. Prior Authorizations Review
D. Market News and Updates
E. Utilization Details

Items to be presented by Dr. Le, Dr. Muchmore, Chairman

9. Action Item – Vote to Update ADHD/Narcolepsy Prior Authorization Criteria – See Appendix G.

A. Evaluation of New Products
B. COP Recommendations

Items to be presented by Dr. Sipols, Dr. Muchmore, Chairman

10. 30 Day Notice to Prior Authorize Topical Corticosteroids – See Appendix H.

A. COP Recommendations

Items to be presented by Dr. Le, Dr. Muchmore, Chairman

11. Questions Regarding Posted 30 Day Notices – See Appendix I.

A. 30 Day Notice to Prior Authorize Adcirca®
B. 30 Day Notice to Prior Authorize Physician Administered Medications, including Benlysta®
C. 30 Day Notice to Prior Authorize Colcrys® and Uloric®
D. 30 Day Notice to Prior Authorize Miscellaneous Bladder Agents
E. 30 Day Notice to Prior Authorize Neudexta™
F. 30 Day Notice to Prior Authorize Testosterone Replacement Products

Items to be presented by Dr. Graham, Dr. Muchmore, Chairman

12. FDA and DEA Updates – See Appendix J.

13. Future Business

A. Utilization Review of Diabetes Products
B. Annual Review of Anxiolytics
C. Annual Review of Antiemetics
D. Annual Review of Otic Antibiotics
E. New Product Reviews

14. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of APRIL 13, 2011

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.: Vice-Chairman	X	
Mark Feightner, Pharm.D.		X
Anetta Harrell, Pharm.D.	X	
Evelyn Knisely, Pharm.D.	X	
Thomas Kuhls, M.D.	X	
John Muchmore, M.D., Ph.D.: Chairman	X	
Paul Louis Preslar, D.O., MBA	X	
James Rhymer, D.Ph.	X	
Bruna Varalli-Claypool, MHS, PA-C	X	
Eric Winegardener, D.Ph.		X

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Metha Chonlahan, D.Ph.; Clinical Pharmacist		X
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	X	
Ronald Graham, D.Ph.; Pharmacy Director	X	
Shellie Keast, Pharm.D, M.S..; DUR Manager	X	
Chris Le, Pharm.D.; Clinical Pharmacist/Coordinator	X	
Carol Moore, Pharm.D.; Clinical Pharmacist	X	
Neeraj Patel, Pharm.D.; Clinical Pharmacist	X	
Lester A. Reinke, Ph.D.; Associate Dean for Graduate Studies & Research	X	
Leslie Robinson, D.Ph.; PA Coordinator		X
Jennifer Sipols, Pharm.D.; Clinical Pharmacist	X	
Visiting Pharmacy Student(s): Stephanie Harp, Natasha Goli	X	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Mike Fogarty, J.D., M.S.W.; Chief Executive Officer		X
Nico Gomez; Director of Gov't and Public Affairs		X
Garth Splinter, M.D., M.B.A.; Director of Medicaid/Medical Services	X	
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	X	
Howard Pallotta, J.D.; Director of Legal Services		X
Rebecca Pasternik-Ikard, Deputy State Medicaid Director	X	
Lynn Rambo-Jones, J.D.; Deputy General Counsel III	X	
Rodney Ramsey; Drug Reference Coordinator	X	
Jill Ratterman, D.Ph.; Pharmacy Specialist	X	
Kerri Wade, Senior Pharmacy Financial Analyst	X	

OTHERS PRESENT:		
Kathleen Karnik, OMJ SA	Dan Davis, MHAT	David Williams, Forest
Jim Dunlap, Lilly	Carol A. Curtis, AstraZeneca	Janie Huff, Takeda
Holly Turner, Merck	Jeff Himmelberg, GSK	Warner Quua, GSK
James Osborne	Don Kempin, Novo Nordisk	Ben Liniger, Alcon
Warren Tyes, Merck	Mike, Ketcher, Novo Nordisk	Mark DeClerk, Lilly
Donna Erwin, Bristol Myers Squibb	David Mershon, Bristol Myers Squibb	Charlene Kaiser, Amgen
Russ Wilson, OMJ PI	Jim Chapman, Abbott	Pat Trahan, Taro

PRESENT FOR PUBLIC COMMENT:		
Agenda Item No. 5	Brad Clay, Pharm.D.; Amgen	
Agenda Item No. 8	James Osborne, Pharm.S.; GlaxoSmithKline	Golden Zenon, Pharm.D.; Merck
Agenda Item No. 11	Shawn Boykin, Ph.D.; Eli Lilly	

AGENDA ITEM NO. 1: CALL TO ORDER

1A: Roll Call

Dr. Muchmore called the meeting to order. Roll call by Dr. Graham established the presence of a quorum.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 2: PUBLIC COMMENT FORUM

Dr. Muchmore acknowledged the speakers for public comment:

Agenda Item No. 5 Brad Clay, Pharm.D.; Amgen

Agenda Item No. 8 James Osborne, Pharm.D.; GlaxoSmithKline
Godden Zenow, Pharm.D.; Merck

Agenda Item No. 11 Shawn Boykin, Ph.D.; Eli Lilly

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: APPROVAL OF DUR BOARD MINUTES

3A: March 9, 2011 DUR Minutes

Dr. Kuhls moved to approve as submitted; seconded by Ms. Varalli-Claypool.

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON DUR/MEDICATION COVERAGE AUTHORIZATION UNIT

4A: Retrospective Drug Utilization Review: December 2010

4B: Retrospective Drug Utilization Review Response: November 2010

4C: Medication Coverage Activity Audit: March 2011

4D: Pharmacy Help Desk Activity Audit: March 2011

Reports included in agenda packet; presented by Dr. Keast.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO UPDATE OSTEOPOROSIS PBPA CRITERIA AND PRIOR AUTHORIZE PROLIA™ AND ATELVIA™

For Public Comment: Brad Clay, Pharm.D.: Good evening, I'm Brad Clay. I'm a Pharm.D. Medical Liaison in Amgen Scientific Affairs department and I want to speak to you guys and ladies about Prolia, or denosumab. I know that I saw your publication from last month. I know obviously you have the clinical data, looked up the PI, you referenced the AACE guidelines, so I'm just going to highlight a couple of things for your consideration and then just ask a question that we're interested in for clarification's sake. So first of all, just to point out, there's two basic indications for Prolia. One is for postmenopausal women, so there's a specific patient right there, and then the women either have to be at high risk for fracture or which by definition means they've had a prior fracture when they have multiple risk factors for fracture, or the second indication is that they have become intolerant to other available osteoporosis therapy. So that's the FDA indication. I want to talk briefly about the molecule itself. It's monoclonal antibody. It has a different mechanism of action, and it is in a different class than the bisphosphonates or the estrogens or bone forming agents such as teriparatide, a different class. It works by a 2-step process. Its' target is RANK ligand and basically Prolia is a monoclonal antibody against RANK ligand. RANK ligand is a growth factor for osteoclasts, so in a 2-step process, number one, it prevents the differentiation and maturation of precursor osteoclasts into osteoclasts, and the second inhibition is that it inhibits mature osteoclasts from becoming activated and attaching to the bone and beginning the remodeling process. So very different from all the other available therapies. Let me briefly review the Phase III data which led to its' approval, one huge trial, over 7800 patients, placebo controlled looking at fracture as an endpoint. At three years it was shown to reduce the relative risk of fractures by 68% and at the spine by 20% and in non-vertebral fractures, and by 40% for hip fractures. I want to point out that all the other osteoporosis therapies at this point have not shown that with the exception of intravenous zoledronic acid. All the other ones either can only prove from a single study either a reduction of spine fractures or two out of the three of the spine, nonvertebral and hip fractures. And then we do have in two other Phase III studies, head to head data with alendronates which was given weekly. These trials were very large as well, one trial being over 600 patients, the other trial being a little less than 1200 patients. These trials did not have fracture as an endpoint but they did have bone mineral density, which of course is one of the major predictors for fracture along with age and having a prior fracture. In both of those studies, Prolia showed statistically significant superiority in terms of raising bone mineral density over generic alendronate. Let me in the interest of fair balance, point out that there is important safety information to consider; established hypocalcemia is a contraindication and all patients should be on calcium and vitamin D. Patients who experienced hypocalcemia, most of those patients were not receiving calcium and vitamin D. Because RANK ligand also, there are RANK ligand receptors on monocytes and macrophages. The FDA was very careful to look at infection rates with Prolia and I just want to point out that there are increased risks of infections although not statistically significantly so. In the label, basically serious infectious events were 3.3% in the placebo arm and 4.0% in the Prolia arm. Neoplasms or malignancies, there were 4.3% new malignancies in placebo arm, versus 4.8% in the Prolia arm. Osteonecrosis of the jaw is another important warning that the PI points out. To this point in the osteoporosis setting, there's only been two patients worldwide who have experienced ONJ with Prolia. So that's, I'm going to stop with my overall comments right there and just ask a question for clarification's sake. Looking at your

recommendation that you received and recognizing that there is a generic bisphosphonate on the market, we recognize that Prolia may not always be a first line choice, although the AACE guidelines point out that it can be, but the market reality is you do have a generic bisphosphonate in place and so the question we just wanted to ask is based upon your interpretation of the recommendations, is Prolia available for patients once they fail a bisphosphonate? The reason behind my question is we have here new products with a different mechanism of action with head to head superiority at least in terms of bone mineral density so it would seem to make sense that instead of simply trying another agent in the same class, why not try a different agent. And of course I'd love to try to answer any questions you may have on Prolia as well.
Materials included in agenda packet; presented by Dr. Patel.
Dr. Bell moved to approve as submitted; seconded by Dr. Preslar.
ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: 60-DAY NOTICE TO PRIOR AUTHORIZE TOPICAL CORTICOSTEROIDS
Materials included in agenda packet; presented by Dr. Sipols.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 7: 30-DAY NOTICE TO PRIOR AUTHORIZE PRADAXA®
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 8: ANNUAL REVIEW OF ADVAIR® AND SYMBICORT® AND 30-DAY NOTICE TO PRIOR AUTHORIZE DULERA®

For Public Comment; James Osborne, Pharm.D.: Good evening. Thanks for the opportunity to speak. I realize it's 15 minutes until the basketball game, so I'm going to try to keep this brief. Just wanted to highlight some of the label revisions to salmeterol or Serevent Diskus. It's been incorporated into the packet. I just wanted to reinforce these on behalf of GlaxoSmithKline. I'm with the medical liaison out of our medical affairs group. And again, the proposed labeling revisions that the FDA made in February 2010 changed slightly in the final label book. I think they were essentially the same so as monotherapy agents they're clearly contraindicated in asthma. They do reinforce that they should only be used in patients who cannot be controlled on as asthma controller like a low to medium dose of inhaled corticosteroids. Now where the February 2010 recommendations or proposals differ from the final label is that they don't mention using for the shortest duration possible. So it's tweaked slightly. What they say is once the asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy may be discontinued along with the beta-agonist if it can be done without losing asthma control. I did want to comment on the proposed prior authorization to the single LABA, single products. Before I get into that, just real quick, frankly surprised at the number of members you have receiving the monotherapy products, especially in the below 19 …… .. I don't know what the number is for appropriate use, but it, my guess would have been less than 200. In terms of the prior authorization, it's clearly appropriate to use these drugs as monotherapy in COPD, not in asthma; so would ask the Board to consider allowing Serevent at age 4, since that is its' FDA approved indication. Once they've established a need not to limit its' duration, but certainly encourage regular assessment and step-down when warranted, we're sending out "Dear HCP" letters as a part of the REMS program, so we're trying to reinforce that. But what I wanted to focus your attention on the most is who really needs it. There's now three fixed dose combination products. The recommendations are pretty clear that in pediatric and adolescent patients that those should be used unless there's some reason you can't use a fixed dose combination and that you should insure adherence to both if they can't be on the fixed dose combination. I'm a little bit concerned that just the plan to be on inhaled steroids with a long acting beta-agonist may not be enough. Our health outcomes group has published claims analyses and what we see is that patients do refill fluticasone inhaler as often as they refill their salmeterol inhaler, it's just not during the same month. So unless, if they're not using the fixed dose inhaler, just starting out with the plan to be on combination therapy, the patient may not actually do that. Now obviously, refill persistence is not adherence, but they have to have it available to use it concurrently; so I would ask the Board to look at the patients, clearly 19 or under, whoever was getting it for asthma, to see if you can identify overlap in their inhaled corticosteroid prescriptions. I'd be happy to answer your questions.
Dr. Graham: James I have a question. I see where Advair Diskus expiration date is 2011. Can you tell me why there won't be any generics on that particular product?
Dr. Osborne: Yeah, Ron, I've literally been on teleconferences with patent attorneys trying to tell me when the patent expires. There's multiple patents on Advair Diskus. I don't know when all of them expire. I'm sure one of them expires this year. We pay attention to who's developing a generic competitor and the only company that was developing a generic that we were aware of has publicly announced they've cancelled that program, so it's very, this is different from stamping a tablet or filling a capsule. So they do have the technology to deliver aerosolized medication is very difficult and expensive, so just because the patent's expired doesn't mean there will be a generic. I would expect that there would be branded alternatives, but not generic, because the AD rating, the bioequivalence with the inhaled medications are very difficult to establish.
Dr. Graham: Most of our usage is with the Diskus versus HFA.
Dr. Osborne: Absolutely, as we would expect. I mean it has an age indication down to 4, the HFA product is only indicated down to age 12, so it's clearly your population; plus it's been available longer and has a larger use.
Dr. Kuhls: Please, don't miss Thunder. I agree with you totally. I don't understand this usage demographics at all.
Dr. Osborne: Yeah, I would have thought if I saw any in your population it would have been on the far right hand side. Again, the reason it's on the market and they're allowing for two, is there are clinical scenarios we can all conceive of where you need separate inhalers. I'm just surprised at the numbers.

Dr. Kuhls: Yeah, so am I.
For Public Comment; Golden Zenon, Pharm.D.: Good evening. My name is Golden Zenon and I'm a health science associate with Merck. This is our first introduction of Dulera to the committee and my objectives are that introduction as well as just some comments on our clinical studies that were used for approval. And basically Dulera is a fixed dose combination, the third on the market as stated. With that, it is a combination of mometasone furoate combined with formoterol fumarate dihydrate, and it is indicated for asthma patients 12 years of age and older and it is not indicated for the relief of acute symptoms as you know. There are two strengths currently that are available commercially. We've got a 100mcg/5mcg combination as well as a 200mcg/5mcg. These are delivered with two puffs twice a day and every day is the dosage. It is a metered dose inhaler with a counter on it and so for patient understanding and dosage administration, that's available for our patients. Because of the LABA component, it does carry a blackbox warning, similar to all agents in this class; this is the FDA guideline. Dulera should only be prescribed for patients whose asthma is not adequately controlled and currently on long-term controllers, if you will. Our clinical studies followed the FDA guidelines and policy in that a fixed-dose combination product when combined in a single dose, each of those have to basically adhere to the claim of clinical effects in the dosage of each component, look for the amount, frequency and duration and as such, this combination has to demonstrate effectiveness and safety as a combined component. So with that, our safety and efficacy trials were done with 1500 patients and with that, we had a medium dose and a high dose controller if you will, and with that our primary endpoints were two. We derived based on the formoterol component that the ones that were sustained, that were measured serially with an area under the curve at Week 12, twelve hours after the dosage, that effect was maintained at that 12-week period and to the 26-week period of the first trial. The second primary outcome was the clinical reduction in deterioration or the reduction in lung function. This is a reflection of the mometasone component, thereby by definition, the FEV-1 decrease of less than 20%, a peak flow of less than 30%, hospitalizations, emergency room visits or interaction, intervention with an oral steroid dose was that criteria for clinical deteriorations. And so with that, patients who did receive Dulera did show significant improvement over our placebo group. With regard to secondary outcomes, decreased beta agonist use on the short term side, nighttime awakening, decreased quality of life were some of the secondary endpoints derived. So with that in summary, I'll just state that Dulera has been on the market since June of 2010. It's been available since July of that time, and with that we've been very excited to get in this market and obviously, derive outcomes that were derived from our clinical studies and with that, we would look forward to managing cases going forward. So with that, I'll be happy to answer any questions.
Materials included in agenda packet; presented by Dr. Le.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF ANTI-MIGRAINE MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE SUMAVEL®
Materials included in agenda packet; presented by Dr. Sipols.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: FISCAL YEAR 2010 ANNUAL REVIEW
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: ANNUAL REVIEW OF PLAVIX®AND EFFIENT®
For Public Comment; Shawn Boykin, Ph.D.: Good evening Dr. Muchmore and committee members. I'm Dr. Shawn Boykin. I am a cardiovascular epidemiologist by training and I work for Eli Lilly. One caveat that I do need to make before I give my testimony is that Lilly takes safety seriously and so I do have copies of the PI for Effient on hand should you require a copy of it. But in terms of the comment that I want to make is that I'd to compliment Shellie and her staff on how well thought out and structured the PA is for Effient. Of couple of highlights that I want to point out, number one, is that the PA is very much consistent with the Effient indication. Secondly the PA does provide for consistency and continuity of care between an in-patient and an out-patient setting. As I'm sure you're all aware, many of the current events take place within those first few days, the first week after PCI, so having the drug immediately available to patients when they're transitioned home is important and that's included in the PA here. And the third thing that I want to highlight is the fact that the PA, the approval of 12 months is very much consistent with the guidelines that have been put forth by the American College of Cardiology, the American Heart Association for both unstable angina and NSTEMI as well as STEMI. And just as a note the UA and STEMI guidelines were just recently updated, 2011, just about 15 days ago, and both of those sets of guidelines are important. They do recommend maintenance dose therapy either using prasugrel or clopidogrel for 12 months. They also do recommend consideration beyond 15 months of maintenance dose therapy with either drug for patients who have received a drug eluding stent. I just wanted to bring that to your attention. There has been quite a bit of novel research that's been published this year regarding pharmacogenomics in this class and so I'd be happy to answer any questions that you might have about that information or any questions that you have pertaining to Effient; but I'd like to yield the rest of my time back to the committee.
Materials included in agenda packet; presented by Dr. Keast.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: ANNUAL REVIEW OF FIBROMYALGIA MEDICATIONS
Materials included in agenda packet; presented by Dr. Patel.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: FDA & DEA UPDATES
Materials included in agenda packet; presented by Dr. Graham.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: FUTURE BUSINESS
Materials included in agenda packet; submitted by Dr. Graham.
A: Utilization Review of Diabetes Products
B: Annual Review of Ophthalmic Antibiotics
C: Annual Review of Antiemetics
D: New Product Reviews
ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: ADJOURNMENT
The meeting was adjourned at 7:33 p.m.

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: April 14, 2011

To: Nancy Nesser, Pharm.D., J.D.
Pharmacy Director
Oklahoma Health Care Authority

From: Shellie Keast, Pharm.D., M.S.
Drug Utilization Review Manager
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of April 13, 2011

Recommendation 1: Vote to Update the Osteoporosis Product Based Prior Authorization Criteria and Prior Authorize Prolia™ (denosumab) and Atelvia™ (risedronate)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends placement of Atelvia™ (risedronate) and Prolia™ (denosumab) into Tier 3 of the Osteoporosis PBPA Category and make the changes to the current criteria noted in red below. The College also recommends sending letters to providers suggesting a drug holiday per AACE recommendations.

Tier 1*	Tier 2	Tier 3
Alendronate (Fosamax®) Calcium + Vitamin D†	Alendronate + D (Fosamax®+D) Ibandronate (Boniva®) Risedronate (Actonel®)	Zoledronic acid (Reclast®) Teriparatide (Forteo®) Risedronate delayed release (Atelvia™) Denosumab (Prolia™)

1. Treatment failure with all lower tiered products, or
2. Contraindication to all lower tiered products, or
3. Allergic reaction to all lowered tiered products, or

4. Specific indication not covered by a lower tiered product.
5. No concomitant use of bisphosphonate therapy will be approved. No additional bisphosphonate may be approved for 365 days following zoledronic acid infusion.
6. Clinical Exceptions/Additional Criteria:
    a. Risedronate may be approved for members with high risk for gastric side effects.
    b. Zoledronic acid may be approved for members with a diagnosis of Paget's disease or for osteoporosis if secondary diagnosis meets criteria below:
        i. Severe esophageal disease (e.g., ulcerations, strictures)
        ii. Inability to take anything by mouth
        iii. Inability to sit or stand for prolonged periods
        iv. Inability to take an oral bisphosphonate for other special medical circumstances that justify the method of administration
    c. Teriparatide requires a BMD test (T-score at or below -2.5) within the last month, and a minimum 12 month trial with a bisphosphonate plus adequate calcium and vitamin D, and a 12 month trial of Prolia™ (Denosumab), unless contraindicated, intolerant, or allergic, that did not yield adequate results.
7. Quantity Limits apply bases on FDA maximum doses.

Additionally, the Drug Utilization Review Board notes that they are aware of the potential benefit of teriparatide for fracture healing.

Recommendation 2: Annual Review of Advair® (fluticasone/salmeterol) and Symbicort® (budesonide/formoterol) and 30 Day Notice to Prior Authorize Dulera® (mometesone/formoterol) and Long-Acting Beta Agonists (LABAs)

NO ACTION REQUIRED.

The College of Pharmacy does not recommend any changes to the criteria for the currently prior authorized combination products at this time.

Recommendation 3: Annual Review of Anti-Migraine Products and 30 Day Notice to Prior Authorize Sumavel® (sumatriptan)

MOTION TABLED.

Recommended changes will be voted on at next meeting along with addition of new product.

Recommendation 4: Annual Review of Plavix® (clopidogrel) and Effient® (prasugrel)

NO ACTION REQUIRED.

The College of Pharmacy does not recommend any changes at this time.

Recommendation 5: Annual Review of Fibromyalgia Medications

NO ACTION REQUIRED.

The College of Pharmacy does not recommend any changes at this time.

Appendix B

RETROSPECTIVE DRUG UTILIZATION REVIEW REPORT
March 2011

MODULE	DRUG INTERACTION	DUPLICATION OF THERAPY	DRUG-DISEASE PRECAUTIONS	DOSING & DURATION
Total # of messages	58,901	70,939	1,187,750	34,784
Limits applied	Established, Major, Males and Females, Age 36-50	Duplication in benzodiazepines, Age 21-28	Contraindicated, Males and Females, Drug Dependence, Age 0-150	High Dose, NSAIDs, Males & Females, Age 50-150
Total # of messages after limits were applied	100	127	102	85
Total # of members reviewed	100	118	81	84

LETTERS

Category	Prescribers	Pharmacies	Total Letters
Drug Interaction	12	0	12
Duplication of Therapy	29	17	46
Drug-Disease Precautions	12	0	12
Dosing & Duration	28	3	31
Total Letters Sent	81	20	101

Retrospective Drug Utilization Review Report

Claims Reviewed for December 2010

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 0-18	NSAIDs, Males and Females, Age 50-150	Contraindicated, Chronic Liver Disease, Males and Females, Age 30-50	High & Low Dose, Duration, Statins Males and Females, Age 0-150

Response Summary (Prescriber)
Letters Sent: 58
Response Forms Returned: 32

The response forms returned yielded the following results:

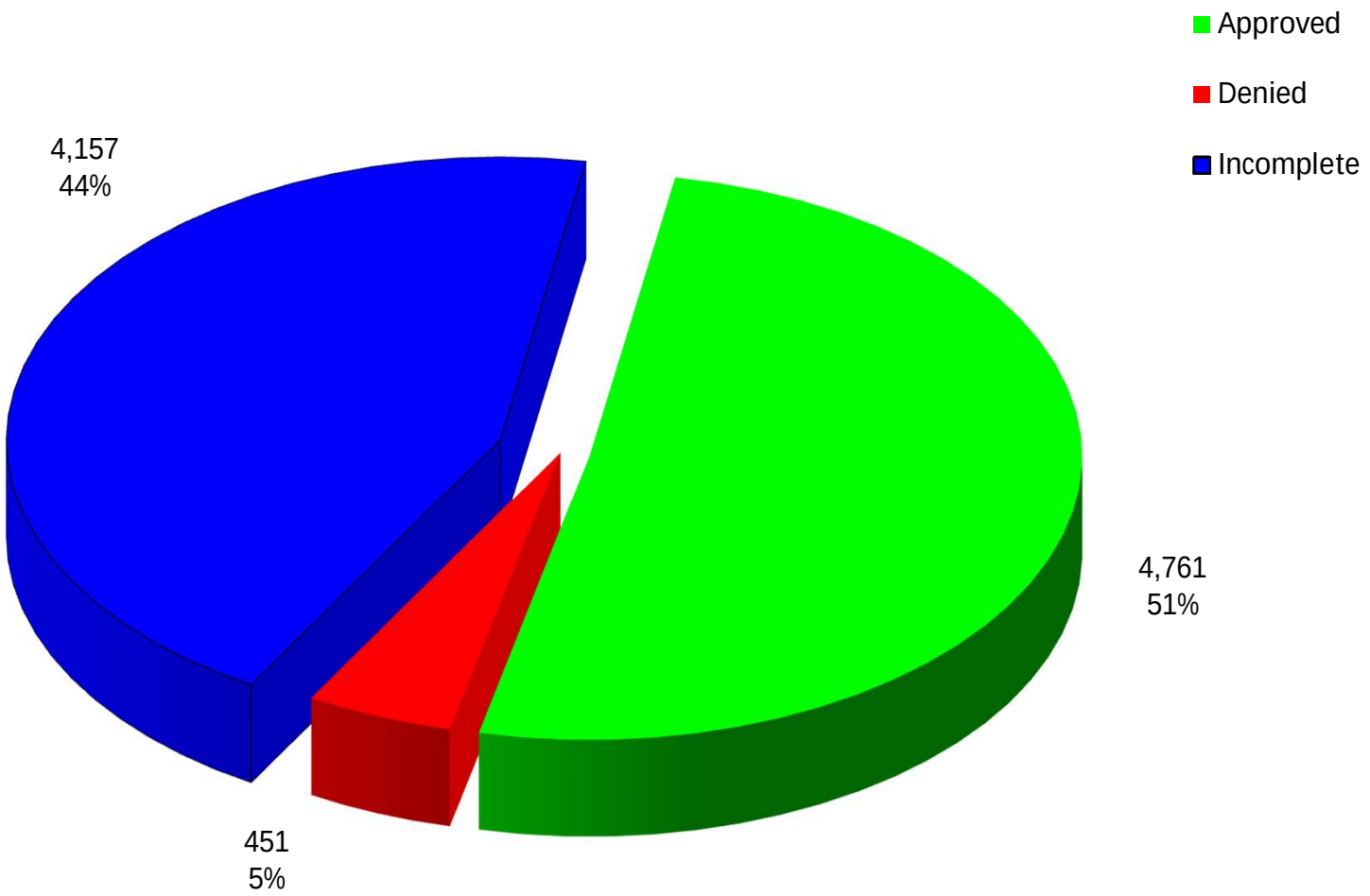
1 (3%)	*Record Error—Not my patient.*
3 (9%)	*No longer my patient.*
3 (9%)	*Medication has been changed prior to date of review letter.*
10 (31%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
10 (31%)	*I am aware of this situation and will plan to continue monitoring therapy.*
5 (16%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 14
Response Forms Returned: 14

The response forms returned yielded the following results:

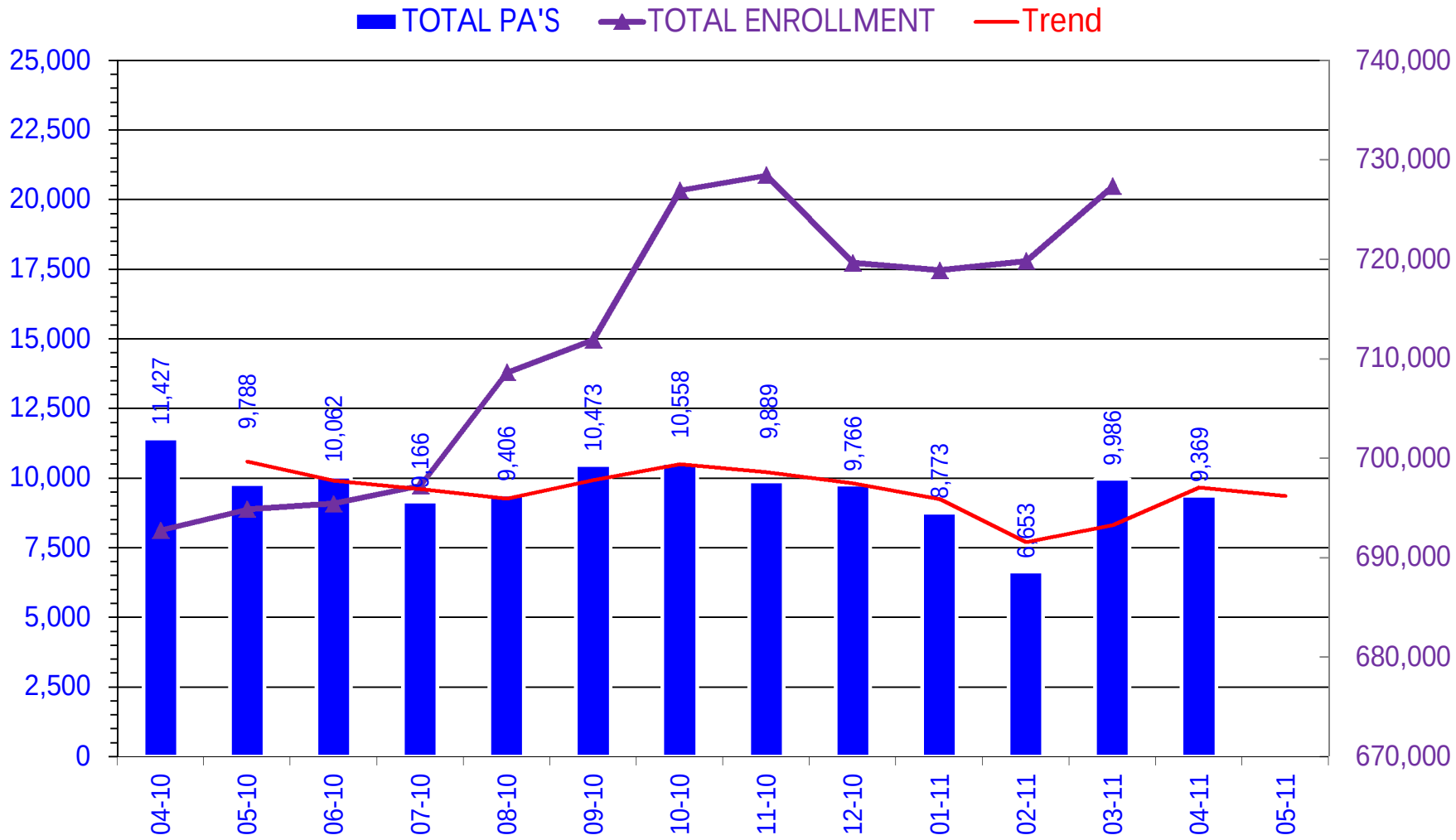
0 (0%)	*Record Error—Not my patient.*
0 (0%)	*No longer my patient.*
1 (8%)	*Medication has been changed prior to date of review letter.*
6 (43%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
2 (14%)	*I am aware of this situation and will plan to continue monitoring therapy.*
5 (36%)	*Other*

PRIOR AUTHORIZATION ACTIVITY REPORT: April 2011



PA totals include overrides

PRIOR AUTHORIZATION REPORT: April 2010 – April 2011



PA totals include overrides

Prior Authorization Activity

April 2011

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort	426	174	7	245	361
Amitiza	25	9	2	14	211
Anti-Ulcer	354	79	25	250	101
Antidepressant	365	133	17	215	342
Antihistamine	412	239	12	161	326
Antihypertensives	79	22	4	53	311
Antimigraine	79	29	3	47	352
Atypical Antipsychotics	622	330	7	285	356
Benzodiazepines	96	45	0	51	227
Bladder Control	66	16	3	47	362
Brovana (Arformoterol)	2	1	0	1	361
Byetta	8	5	0	3	361
Elidel/Protopic	71	24	5	42	91
ESA	126	98	2	26	81
Fibromyalgia	129	39	11	79	311
Fortamet/Glumetza	1	0	0	1	0
Forteo	4	0	0	4	0
Glaucoma	25	15	0	10	363
Growth Hormones	48	39	2	7	154
HFA Rescue Inhalers	87	36	4	47	311
Insomnia	94	20	6	68	126
Misc Analgesics	25	2	18	5	363
Muscle Relaxant	144	53	44	47	82
Nasal Allergy	354	105	25	224	112
NSAIDS	143	28	8	107	342
Ocular Allergy	160	24	9	127	106
Ocular Antibiotics	60	10	1	49	14
Opioid Analgesic	290	151	15	124	243
Other	774	333	79	362	243
Otic Antibiotic	88	46	1	41	19
Pediculicides	128	67	13	48	17
Plavix	246	165	0	81	297
Qualaquin (Quinine)	2	0	0	2	0
Singulair	991	521	24	446	257
Smoking Cessation	48	12	2	34	39
Statins	101	39	7	55	362
Stimulant	1,087	600	42	445	287
Symlin	7	1	2	4	363
Synagis	13	0	13	0	0
Topical Antibiotics	9	1	0	8	27
Topical Antifungals	30	2	3	25	19
Ultram ER and ODT	8	2	1	5	178
Xolair	4	2	0	2	363
Xopenex Nebs	33	12	2	19	348
Zetia (Ezetimibe)	21	13	0	8	362
Emergency PAs	4	4	0	0	
Total	**7,889**	**3,546**	**419**	**3,924**	

Overrides					
Brand	40	25	1	14	204
Dosage Change	600	574	1	25	7
High Dose	9	8	0	1	178
IHS-Brand	1	1	0	0	359
Ingredient Duplication	11	11	0	0	9
Lost/Broken Rx	88	82	4	2	4
NDC vs Age	15	13	0	2	278
Nursing Home Issue	84	81	0	3	6
Other	24	21	1	2	19
Quantity vs. Days Supply	603	394	25	184	273
Stolen	4	4	0	0	25
Third Brand Request	1	1	0	0	10
Overrides Total	**1,480**	**1,215**	**32**	**233**	
Total Regular PAs + Overrides	**9,369**	**4,761**	**451**	**4,157**	

Denial Reasons

Unable to verify required trials.	3,205
Lack required information to process request.	999
Does not meet established criteria.	425

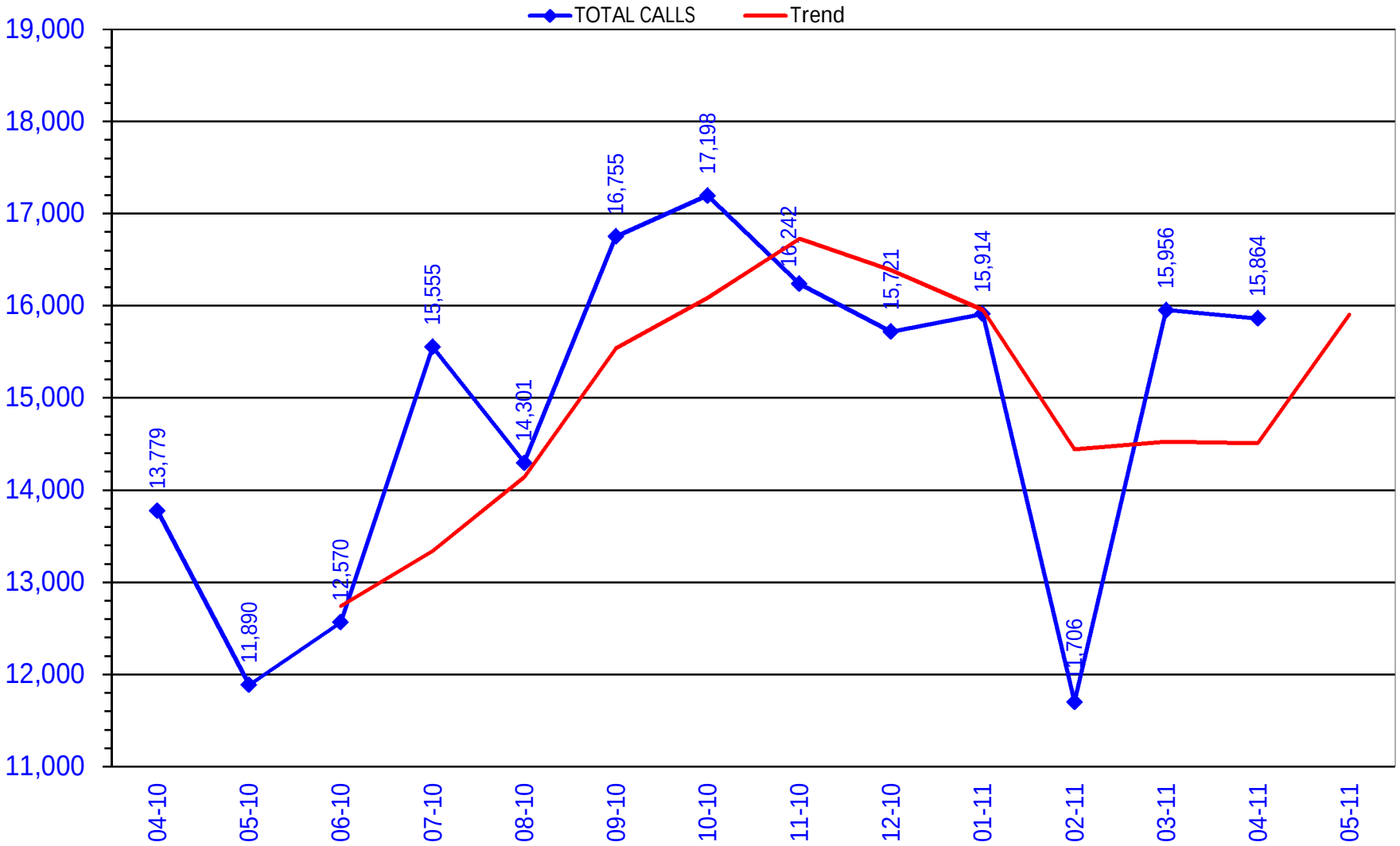
Duplicate Requests: 613

Letters: 1,479

No Process: 383

Changes to existing PAs: 386

CALL VOLUME MONTHLY REPORT:
April 2010 – April 2011



Appendix C

Vote to Prior Authorize Pradaxa® (dabigatran etexilate mesylate)

Oklahoma Health Care Authority, May 2011

Recommendation

The College of Pharmacy recommends prior authorization of Pradaxa® (dabigatran etexilate mesylate) requiring an FDA approved indication (special consideration will be given for a diagnosis of DVT when warfarin is not a viable option).

Appendix D

Vote to Prior Authorize Dulera® (mometasone/formoterol) and Update Criteria

Oklahoma Health Care Authority
May 2011

Utilization of Long Acting Beta Agonists (LABAs)

Upon the request of the DUR Board, utilization data for salmeterol and formoterol products were analyzed for January through March 2011, the most recent quarter available for analysis. Each month was analyzed separately and below are the percentages of members with a paid claim for salmeterol or formoterol and a paid claim for an inhaled corticosteroid product within the same month:

- January - 51% (of the 49% who had a paid claim for LABAs only, 5 were under 18 years of age)
- February - 62% (of the 38% who had a paid claim for LABAs only, 7 were under 18 years of age)
- March - 43% (of the 57% who had a paid claim for LABAs only, 6 were under 18 years of age)

The National Asthma Education and Prevention Program (NAEPP) guidelines[1] recommend routine monitoring once asthma control is achieved as asthma often varies over time. A step down in therapy may be possible to identify the minimum medication necessary to maintain control.

Conclusion and Recommendations

The College of Pharmacy recommends prior authorization of Dulera® (mometasone/formoterol) with the following update to the criteria:

1. Diagnosis of COPD: Approve for one year
2. Diagnosis of Asthma:
    a. Member must be at or above the minimum age indicated, AND
    b. Have used inhaled corticosteroid for at least one month immediately prior, AND
    c. Considered uncontrolled by provider (required rescue medication > 2 days a week (not for prevention of exercise induced bronchospasms) and/or needed oral systemic corticosteroids), OR
    d. Clinical situation warranting initiation with combination therapy due to severity of asthma.
3. A quantity limit of one inhaler per 30 days will apply.

The College also recommends prior authorization of all LABA single products with the following criteria:

1. Diagnosis of COPD: Approve for one year
2. Diagnosis of Asthma:
    a. Member must be 12 years of age or older, AND
    b. Must have used an inhaled corticosteroid for at least one month immediately prior with inadequate results and plan to continue using ICS concomitantly with the LABA.
    c. Reason why member cannot use and ICS/LABA combination product.
    d. Approval will be for only 3 months to ensure use for the shortest duration of time required to achieve control of asthma symptoms.

[1] NAEPP Guidelines: Accessed at: http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf

Appendix E

Vote to Prior Authorize Sumavel® (sumatriptan) and Update Antimigraine PBPA Criteria

Oklahoma Health Care Authority, May 2011

Recommendations

The College of Pharmacy recommends the following changes to the existing tier structure:

1. Placement of Naratripan (Amerge®) into Tier 2.
2. Placement of Sumatriptan (Sumavel DosePro®) into Tier 3.
    a. Must also provide clinical reason why member cannot use all other available formulations of sumatriptan.
3. Existing criteria will apply.

Tier 1	Tier 2	Tier 3
Sumatriptan (Imitrex®)	Naratriptan (Amerge®)	Almotriptan (Axert®) Eletriptan (Relpax®) Frovatriptan (Frova®) Rizatriptan (Maxalt®; Maxalt MLT®) Sumatriptan (Sumavel DosePro®) Sumatriptan/Naproxen (Treximet®) Zolmitriptan (Zomig®; Zomig-ZMT®)

Appendix F

Fiscal Year 2010 Annual Review of Anti-Ulcer Medications

Oklahoma HealthCare Authority
May 2011

Prior Authorization Criteria

Tier 1	Tier 2	Tier 3
omeprazole (Prilosec) pantoprazole (Protonix® Tabs)	dexlansoprazole (Dexilant®) lansoprazole (Prevacid®)*	omeprazole (Prilosec ®40mg caps & Susp)* esomeprazole (Nexium® Caps and I.V.)* lansoprazole (Prevacid ODT)* pantoprazole (Protonix® Susp & I.V.)* rabeprazole sodium (Aciphex® Tabs)
Ranitidine (Zantac® Effervescent Tabs) – must have reason why member cannot take other dosage forms. Pepcid® Suspension (famotidine) – reserved for members less than 1 month old. omeprazole/sodium bicarbonate – only generic products covered, and requires special reason for use. Prevacid NapraPac: see NSAIDs Criteria		

Mandatory Generic Plan Applies, Tiers based on Supplemental Rebates
*Special Formulations including ODTs, Granules, Suspension, and Solution for I.V. require special reason for use.

Criteria for Approval of a Tier-2 medication:

1. A 14-day trial of omeprazole dosed up to 40mg per day (two 20mg caps) that has resulted in inadequate relief of symptoms or intolerable adverse effects.
2. Contraindication to all available Tier 1 medications.
3. An indication not covered by lower tiered medications.

Criteria for Approval of a Tier-3 medication:

1. A 14-day trial all available Tier 2 medications that has resulted in inadequate relief of symptoms or intolerable adverse effects.
2. Contraindication to all available Tier 2 medications.
3. An indication not covered by lower tiered medications.

Criteria for Approval of Age Appropriate PPIs for Pediatric Members under the age of 19:

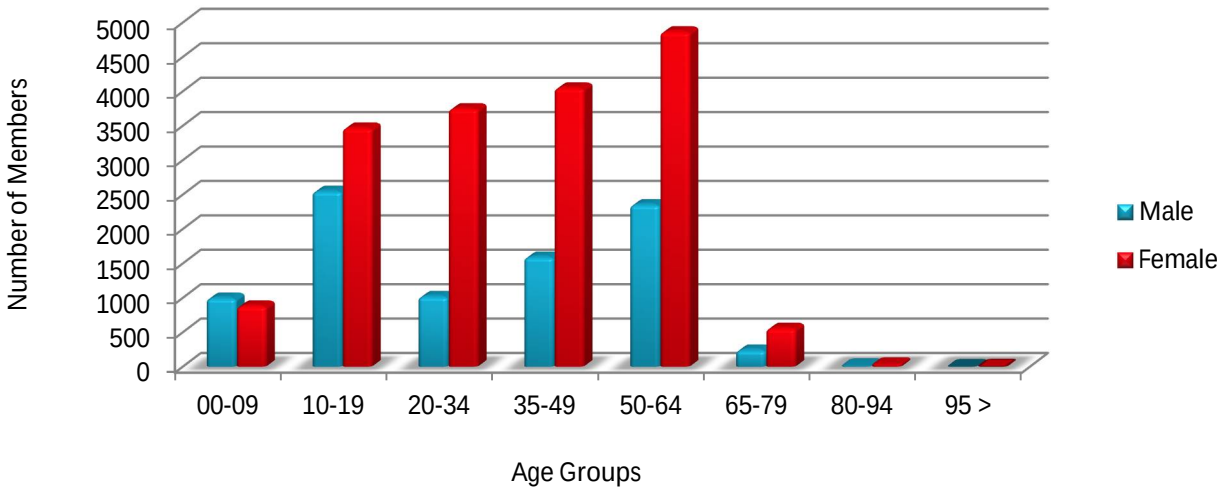
1. A recent 14-day trial of an H_2 receptor antagonist that has resulted in inadequate relief of symptoms or intolerable adverse effects.
2. Recurrent or severe disease such as:
    a. GI bleed
    b. Zollinger-Ellison or similar disease

Trends in Utilization of Proton Pump Inhibitor (PPI) Medications

Comparison of Fiscal Years

Fiscal Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2009	23,582	101,436	$9,423,401.52	$92.90	$2.94	3,827,111	3,204,599
2010	26,418	109,607	$7,134,172.04	$65.09	$2.03	4,266,113	3,506,570
% Change	12.00%	8.10%	-24.30%	-29.90%	-31.00%	11.50%	9.40%
Change	2,836	8,171	-$2,289,229.48	-$27.81	-$0.91	439,002	301,971

Demographics of Members Utilizing PPIs: FY 2010

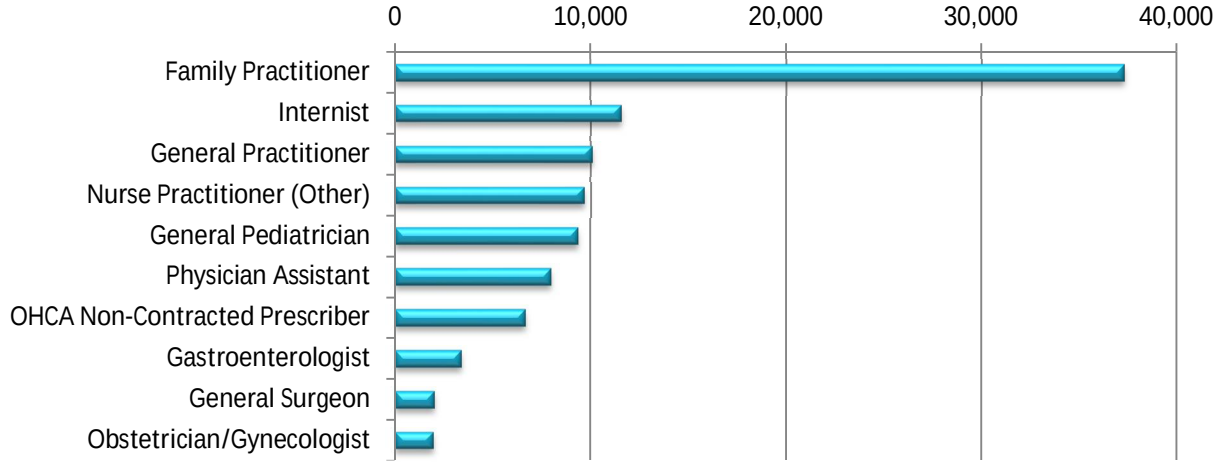


Pediatric PPI Usage

The pediatric criteria was approved by the DUR Board in September 2009 and implemented January 2010. Please note, the last age group contains 4 years.

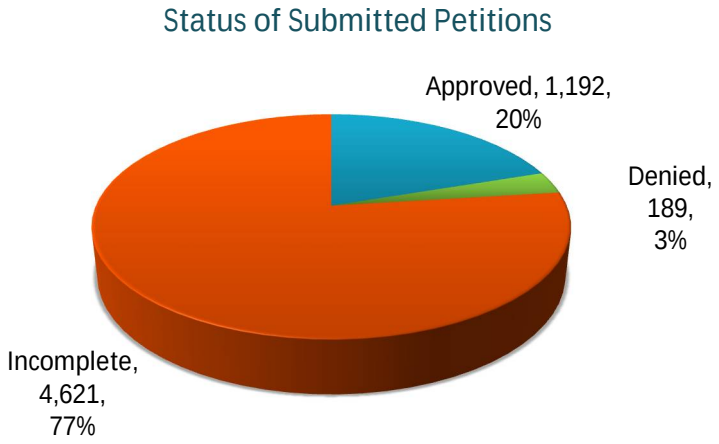
	CY 2009		CY 2010	
AGES	Male	Female	Male	Female
0-2	395	302	374	277
3-5	228	196	205	172
6-8	347	345	301	330
9-11	549	543	539	594
12-14	668	739	688	862
15-18	1220	1862	1234	2005
Total	3,407	3,987	3,341	4,240
	7,394 Total Pediatric Members		7,581 Total Pediatric Members	

The Top Prescribers of PPIs by Number of Claims: FY 2010



Prior Authorizations

There were a total of 6,002 petitions submitted for this PBPA category during fiscal year 2010. Computer edits are in place to detect tier-1 medications in member's recent claims history and generate automated prior authorization where possible. The following chart shows the status of the submitted petitions.



Market News and Update

- Prevacid®24HR (lansoprazole) was available over-the-counter in November 2009
    - Lansoprazole became available in generic November 2009
    - Lansoprazole ODT became available in generic in October 2010; however there are not enough manufacturers yet for the state maximum allowable cost (SMAC) to be applied
- Pepcid® (famotidine) suspension became available in generic on 5/27/10, and SMAC was applied on 7/19/10, however, the cost is still considerably more than ranitidine syrup as there is only one maker.
- In September 2010 FDA required a medication label change to include warning regarding increased risk of osteoporosis related fractures of the hip, wrist, or spine in patients who received high-dose, long-term PPI therapy.
- In November 2009 FDA approved pantoprazole (Protonix®) for short term treatment of erosive esophagitis associated with GERD in pediatric patients, ages five years and older
    - Pantoprazole was moved to tier-1 effective 2/1/2011 due to change in cost making it comparable to the other Tier 1 medication, omeprazole
- Aciphex® (rabeprazole) – anticipated to expire in 2013
- Nexium® (esomeprazole) – anticipated to expire in 2014
- Dexilant® (dexlansoprazole) – anticipated to expire in 2020
    - Effective March 2010, Kapidex™ was renamed Dexilant™ to avoid possible medication errors

Conclusion and Recommendations

While there was an increase in the total number of pediatric members who had claims for PPI's in CY10, there was a small decrease in PPI use in the very young (below 9 years of age.) It should be noted that the overall number of SoonerCare members under the age of 19 increased by approximately 63,000 members from January 2009 to December 2010. The percentage of pediatric members in the overall SoonerCare population remained steady at 66%. The College of Pharmacy recommends the following change to the current criteria:

Criteria for Approval of a Tier-2 medication:

1. A 14-day trial of all available Tier 1 medications titrated up to recommended dose that has resulted in inadequate relief of symptoms or intolerable adverse effects.

Utilization Details of PPI Medications: Fiscal Year 2010

BRAND NAME	CLAIMS	MEMBERS	UNITS	DAYS	COST	UNITS/ DAY	CLAIMS/ MEMBER	% COST
OMEPRAZOLE CAP 20MG	57,835	17,922	2,664,300	1,963,715	$938,197.89	1.36	3.23	13.15%
PREVACID CAP 30MG DR	11,109	3,982	346,828	329,241	$1,861,688.32	1.05	2.79	26.10%
LANSOPRAZOLE CAP 30MG	9,979	2,450	310,792	296,589	$706,999.79	1.05	4.07	9.91%
NEXIUM CAP 40MG	8,489	1,289	261,631	254,250	$1,467,393.36	1.03	6.59	20.57%
PANTOPRAZOLE TAB 40MG	6,521	1,304	198,618	195,002	$520,236.95	1.02	5	7.29%
OMEPRAZOLE CAP 40MG	3,490	1,758	116,047	104,711	$74,178.19	1.11	1.99	1.04%
KAPIDEX CAP 60MG DR	2,571	943	77,065	76,975	$302,542.58	1	2.73	4.24%
PREVACID CAP 15MG DR	2,229	1,017	65,897	65,850	$369,445.41	1	2.19	5.18%
ACIPHEX TAB 20MG	1,739	261	53,388	51,955	$330,652.89	1.03	6.66	4.63%
LANSOPRAZOLE CAP 15MG	1,687	524	49,718	49,905	$119,440.06	1	3.22	1.67%
OMEPRAZOLE CAP 10MG	1,025	429	32,891	30,533	$18,364.85	1.08	2.39	0.26%
PREVACID TAB 15MG STB	984	289	29,119	30,180	$152,771.76	0.96	3.4	2.14%
PREVACID TAB 30MG STB	403	100	12,946	11,916	$69,636.18	1.09	4.03	0.98%
NEXIUM CAP 20MG	400	89	11,963	11,903	$67,066.10	1.01	4.49	0.94%
KAPIDEX CAP 30MG DR	375	167	11,436	11,346	$45,307.50	1.01	2.25	0.64%
DEXILANT CAP 60MG DR	352	249	10,487	10,517	$40,101.67	1	1.41	0.56%
PANTOPRAZOLE TAB 20MG	181	56	5,535	5,310	$15,062.11	1.04	3.23	0.21%
NEXIUM GRA 40MG DR	48	8	1,440	1,440	$6,840.91	1	6	0.10%
PROTONIX PAK	38	11	1,125	1,125	$5,126.13	1	3.45	0.07%
PRILOSEC POW 10MG	27	13	930	840	$4,665.48	1.11	2.08	0.07%
DEXILANT CAP 30MG DR	26	21	780	780	$3,021.90	1	1.24	0.04%
PRILOSEC POW 2.5MG	24	13	735	715	$3,485.13	1.03	1.85	0.05%
NEXIUM GRA 20MG DR	23	7	930	690	$5,218.32	1.35	3.29	0.07%
PROTONIX TAB 40MG	20	4	707	591	$3,150.50	1.2	5	0.04%
PROTONIX INJ 40MG	17	4	41	41	$611.75	1	4.25	0.01%
NEXIUM GRA 10MG DR	14	5	510	420	$2,948.43	1.21	2.8	0.04%
OMEPRAZOLE TAB 20MG	1	1	256	30	$17.88	8.53	1	0.00%
TOTALS	109,607	26,418*	4,266,115	3,506,570	$7,134,172.04	1.22	4.15	100.00%

*Total number of unduplicated members

Utilization Details of Histamine 2 Receptor Antagonists: Calendar Year 2010

BRAND NAME	CLAIMS	MEMBERS	COST	UNITS/ DAY	CLAIMS/ MEMBER	COST/ DAY	% COST
CIMETIDINE TAB 200MG	18	14	$134.14	1.94	1.29	$0.30	0.02%
CIMETIDINE TAB 300MG	213	97	$2,165.26	2.01	2.2	$0.35	0.25%
CIMETIDINE TAB 400MG	697	327	$7,115.99	2.09	2.13	$0.34	0.84%
CIMETIDINE TAB 800MG	138	74	$1,330.92	1.42	1.86	$0.29	0.16%
CIMETIDINE SOL 300/5ML	450	323	$7,374.12	7.23	1.39	$0.65	0.87%
RANITIDINE TAB 150MG	22,135	8,634	$149,213.41	1.82	2.56	$0.22	17.54%
RANITIDINE TAB 300MG	2,109	859	$16,543.15	1.24	2.46	$0.21	1.95%
ZANTAC TAB 25MG EF	5	2	$900.98	3.78	2.5	$6.67	0.11%
RANITIDINE SYP 75MG/5ML	6,131	3,298	$126,279.56	5.16	1.86	$0.74	14.85%
RANITIDINE SYP 15MG/ML	5,566	2,992	$109,426.35	4.85	1.86	$0.70	12.87%
ZANTAC SYP 15MG/ML	8	3	$752.58	4.38	2.67	$3.14	0.09%
RANITIDINE SYP 150/10ML	3	3	$29.49	4.27	1	$0.72	0.00%
RANITIDINE INJ 50MG/2ML	16	1	$270.24	1.05	16	$2.43	0.03%
ZANTAC INJ 25MG/ML	6	2	$131.87	2.26	3	$4.88	0.02%
RANITIDINE INJ 150/6ML	3	3	$229.70	3.74	1	$5.34	0.03%
ZANTAC INJ 25MG/ML	2	1	$116.18	6	2	$8.30	0.01%
ZANTAC INJ 50/50ML	3	3	$23.21	50	1	$7.74	0.00%
FAMOTIDINE TAB 20MG	7,093	3,027	$66,103.11	1.67	2.34	$0.32	7.77%
FAMOTIDINE TAB 40MG	758	355	$7,591.17	1.24	2.14	$0.30	0.89%
PEPCID SUS 40MG/5ML	399	187	$98,074.60	2.87	2.13	$9.69	11.53%
FAMOTIDINE SUS 40MG/5ML	120	49	$14,980.65	2.77	2.45	$5.08	1.76%
FAMOTIDINE INJ 10MG/ML	14	7	$204.22	3.94	2	$1.94	0.02%
NIZATIDINE CAP 150MG	203	67	$4,517.81	1.92	3.03	$0.74	0.53%
NIZATIDINE CAP 300MG	2	2	$39.01	1	1	$0.67	0.00%
NIZATIDINE SOL 15MG/ML	2,320	1,232	$164,858.15	3.65	1.88	$2.30	19.38%
AXID SOL 15MG/ML	834	436	$72,070.89	3.87	1.91	$2.86	8.47%
TOTALS	49,246	20,849	$850,476.76	2.64	2.36	$0.57	100.00%

Appendix G

VOTE TO UPDATE ADHD/NARCOLEPSY CRITERIA

Oklahoma HealthCare Authority
May 2011

Clinical and Economic Evaluation of New ADHD Products

As medication categories age, costs are generally expected to decline as patents expire and generic formulations become available for more products in the category. However, with the ADHD/Narcolepsy category, the costs are expected to increase in the near future. This is due to increasing trends in the diagnosis and treatment of this disorder, along with new products entering the market. The utilization data presented at the January 2011 meeting for the fiscal year 2010 annual review along with the marketing of new products and new indications prompted a further review of this category.

Among the new products recently added to the ADHD treatment choices, Intuniv® (guanfacine extended release) and Kapvay® (clonidine extended release) warrant a closer look. Both guanfacine and clonidine have been available in the United States for several decades. Although their mechanisms of action differ, both guanfacine and clonidine are alpha-2 agonists and both have been used off-label in the pediatric population as alternatives or as adjunctive therapy to stimulants in the treatment of ADHD.[1] In March of 2011, more than a year after it first entered the market, the FDA approved an additional indication for Intuniv®, allowing it to be used as adjunctive therapy to stimulants. So currently, both Intuniv® and Kapvay® are FDA approved for use as mono-therapy or as adjunctive therapy to stimulant medications in the treatment of ADHD.

The efficacy of Intuniv® was demonstrated in two published studies. The first study[2] was an 8 week study comparing fixed dose Intuniv® vs placebo that demonstrated statistically significant change in ADHD rating scales used. The second study[3] was a 9 week study that compared flexible doses of Intuniv®+stimulants vs. placebo+stimulants which demonstrated statistically significant reduction in ADHD rating scales vs placebo + stimulants. The efficacy of Kapvay® was demonstrated in an 8 week randomized clinical trial in which Kapvay® was shown to improve ADHD rating scales when compared to placebo.[4]

Intuniv® and Kapvay® have been shown, via pharmacokinetic studies, to have slightly longer half-lives and a more blunted release, decreasing the peaks and troughs of the medication levels in the body. The following are the listed elimination half-lives:

Medication	Elimination Half-life from Product Label
Guanfacine	17 hours (range 10-30 hours)
Intuniv® (guanfacine extended release)	18 hours (+ or − 4 hours)
Clonidine	12-16 hours
Kapvay® (clonidine extended release)	12.65 hours (+ or − 3.556 hours)

Although the new extended release formulations, Intuniv® and Kapvay®, were developed to improve upon the adverse effect profile of the immediate release products, there are currently no comparative trials evaluating the efficacy or safety of either Intuniv® or Kapvay® to their immediate release counterparts in the treatment of ADHD. In the absence of such data it is not possible to determine if the pharmacokinetic differences translate into an increase in efficacy or decrease in adverse effects.

Regarding their place in therapy, both clonidine and guanfacine immediate release have clinical evidence demonstrating moderate efficacy when used alone or as adjunctive therapy with stimulants for the management of ADHD and ADHD with tic or pervasive developmental disorders.[5,6,7,8,9] Both immediate release clonidine and

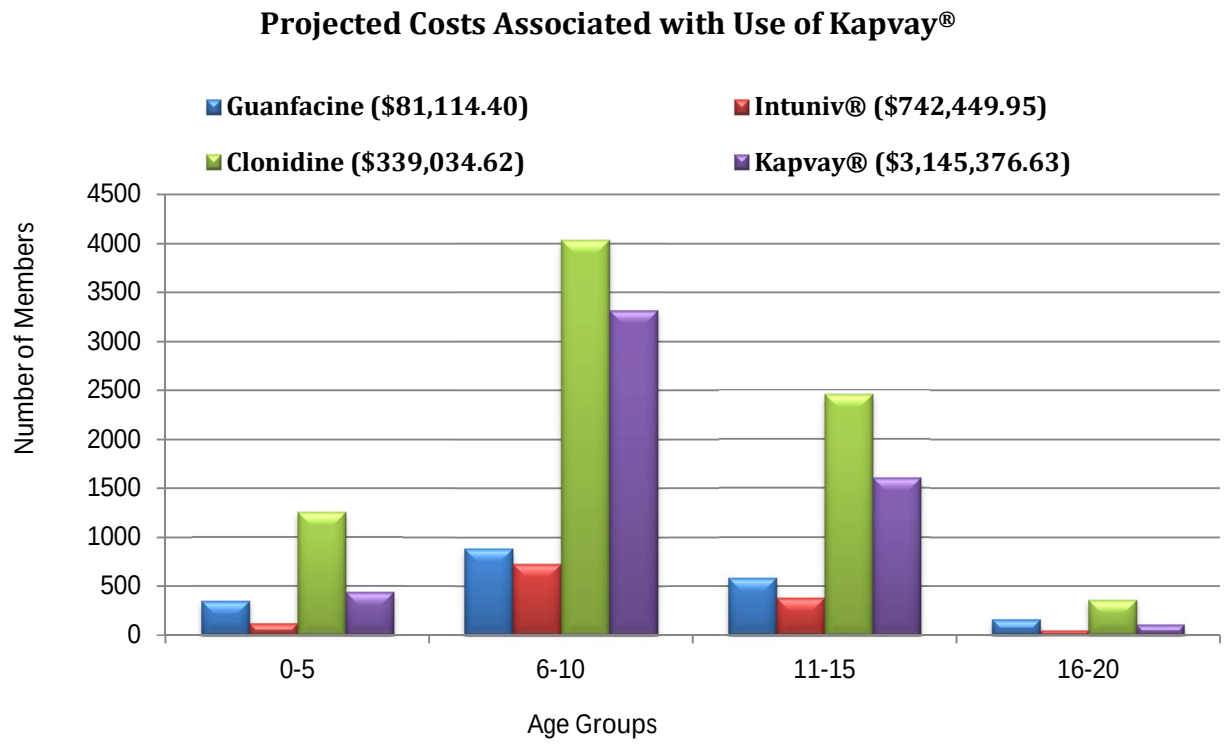
guanfacine have been included in clinical practice guidelines as alternative agents when stimulant medication is not an appropriate option or have failed to produce adequate results.[10,11] The extended release products have yet to be included in clinical practice guidelines.

The following data shows a comparison of costs associated with guanfacine immediate release and Intuniv® for calendar year 2010. Based on the utilization data available for guanfacine and Intuniv® during calendar year 2010, and comparing utilization data of clonidine in the pediatric population, a projection of the costs associated with Kapvay® is presented below.

	Guanfacine immediate release			Intuniv®		
Age Groups	Members	Cost	Cost/Mem	Members	Cost	Cost/Mem
0-5	350	$10,653.31	$30.44	123	$70,383.01	$572.22
6-10	890	$33,735.92	$37.91	732	$416,412.77	$568.87
11-15	584	$26,726.31	$45.76	383	$221,085.34	$577.25
16-20	163	$9,998.86	$61.34	51	$34,568.83	$677.82
		$81,114.40			$742,449.95	

	Clonidine immediate release			Kapvay®*		
Age Groups	Members	Cost	Cost/Mem	Members	Projected Cost	Cost/Mem
0-5	1,254	$37,279.21	$29.73	440	$251,776.62	$572.22
6-10	4,037	$165,755.00	$41.06	3,320	$1,888,829.61	$568.87
11-15	2,453	$107,662.98	$43.89	1,609	$928,634.14	$577.25
16-20	359	$28,337.43	$78.93	112	$76,136.26	$677.82
		$339,034.62			$3,145,376.63	

* At the time of calculation cost data projected based on Intuniv® costs as both products were priced similarly.



CONCLUSIONS AND RECOMMENDATIONS

In remaining consistent with the DUR Board's previous decisions regarding re-formulations of immediate release products currently available as generic formulations, the College of Pharmacy recommends the additional criteria in blue.

Approval of Tier 2 Products:

1. FDA approved diagnosis.
2. Trials of long acting medications from both the amphetamine and methylphenidate category, or a non-stimulant medication if a Tier 2 non-stimulant medication is requested, that did not yield adequate response.
   a. Trials should have been within the last 30-60 days.
   b. Dosed up to maximum recommended dose or provide information regarding side effects at higher dose.
   c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician.
3. Use of Kapvay® also requires recent trial with immediate release clonidine and clinically significant reason why member cannot use immediate release products.
4. Use of Intuniv® also requires recent trial with both immediate release clonidine and guanfacine and clinically significant reason why member cannot use immediate release products.
5. Concomitant use of stimulants and Strattera® is approved only for members with severe disease who have tried multiple stimulant medications alone, titrated to maximum recommended dose, AND the non-stimulant medication alone, titrated to maximum recommended dose, that did not yield adequate response. Concomitant use of stimulants and Intuniv® or Kapvay® will not be covered, due to the availability of the immediate release products without prior authorization.

Tier 1	Tier 2	Tier 3
Amphetamine	Amphetamine	Amphetamine
Adderall®	Vyvanse®	Desoxyn®
Adderall XR®	Methylphenidate	Dexedrine®
Methylphenidate	Metadate ER®	Dexedrine Spansules®
Ritalin®	Metadate CD®	ProCentra™ Oral Solution
Methylin®	Ritalin LA®	Methylphenidate
Ritalin SR®	Non-Stimulant	Daytrana™ Patch
Concerta®	Intuniv® (guanfacine ER)	Non-Stimulant
Focalin®	Kapvay® (clonidined ER)	Provigil® (modafinil)
Focalin XR®		Nuvigil® (armodafinil)
Non-Stimulant		Xyrem® (sodium oxybate)
Strattera® (atomoxetine)		

2011 Tiers based on Net Cost after Supplemental Rebates.
Mandatory Generic Plan Applies.

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Appendix H

30 Day Notice to Prior Authorize Topical Corticosteroid Products

Oklahoma Health Care Authority, May 2011

This category was introduced for possible inclusion in the Product Based Prior Authorization program in March 2011. See the March and April DUR packets for a more complete discussion of the category. This notice and statement of potential economic impact are presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

Recommendations

The College of Pharmacy recommends the addition of the Topical Corticosteroid class of medications to the Product Based Prior Authorization program. The following Tier 1 drug list has been reviewed and determined to be an acceptable combination for use as initial therapy for the majority of members. The College of Pharmacy recommends this list to the Drug Utilization Review Board based on cost and clinical effectiveness for approval before referral to the Oklahoma Healthcare Authority. The following is the proposed Tier list and approval criteria. When Tier 2 products receive a State Maximum Allowable Cost designation and approach the cost of Tier 1 products, they will be moved to Tier 1.

Tier 2 Approval Criteria:

1. Documented trials of ALL Tier 1 topical corticosteroids of similar potency in the past 30 days that did not yield adequate relief.
    a. If Tier 1 trials are completed and do not yield adequate relief, the member must also provide a clinical reason for requesting a Tier 2 in the same potency instead of trying a higher potency.
2. When the same medication is available in Tier 1, a clinical reason must be provided for using a special dosage form of that medication in Tier 2 (foams, shampoos, sprays, kits, etc.).

Topical Corticosteroids	
Tier 1	Tier 2
Ultra high to high potency	
Augmented betamethasone dipropionate (Diprolene AF® G,C)	Amcinonide (O)
Betamethasone dipropionate (Diprosone® O)	Augmented betamethasone dipropionate (Diprolene® O, L)
Clobetasol propionate (Temovate® C,G,O,So)	Clobetasol propionate (Clobex® L,Sh,Spr; Olux® F)
Diflorasone diacetate (Apexicon® O, Apexicon E® C)	Desoximetasone 0.25% (Topicort® C,O,) 0.05% (G)
Fluocinonide 0.025% (Lidex® G,C,O)	Fluocinonide 0.01% (Vanos® C)
Halobetasol propionate (Ultravate® C,O)	Flurandrenolide tape (Cordran®)
	Halcinonide (Halog® C,O)
Med/high to medium potency	
Betamethasone dipropionate (Betanate® C,L)	Amcinonide (Cyclocort® C,L)
Betamethasone valerate (Beta-Val® C,O,L)	Betamethasone dipropionate/calcipotriene (Taclonex® O, Sus, Spr)
Fluocinolone acetonide (Synalar® C,O)	Betamethasone valerate (Luxiq® F)
Fluocinonide emollient (Lidex E® C)	Desoximetasone 0.05% (Topicort LP ® C)
Fluticasone propionate (Cutivate® C,O)	Fluticasone propionate (Cutivate® L)
Hydrocortisone valerate 0.2% C	Hydrocortisone butyrate (Locoid® O,C, L; Locoid Lipo C)
Mometasone furoate (Elocon® O,C,L)	Hydrocortisone probutate (Pandel® C)
Triamcinolone acetonide (Kenalog® C,O,L)	Hydrocortisone valerate (Westcort® C,O)
	Prednicarbate (Dermatop® O,C)
	Triamcinolone acetonide (Kenalog® Spr)
Low potency	
Alclometasone dipropionate (Aclovate® C,O)	Coclortolone pivalate (Cloderm® C)
Desonide (LoKara® C,O,L)	Desonide (Desonate® G, Verdeso® F)
Fluocinolone acetonide (So, C; Derma-Smooth®; Derma-Smooth FS® oil)	Desonide/emollient (Desowyn® kit C,O)
Hydrocortisone acetate 2.5% (C,O,L)	Fluocinolone acetonide (Capex® Sh)
Hydrocortisone/urea (U-Cort® C)	Hydrocortisone acetate 2%/aloe (Nucort®, L)
	Hydrocortisone/lidocaine (LidaMantle HC® C)
C=cream, O=ointment, L=lotion, G=gel, F=foam, So=solution, Sh=shampoo, Spr=Spray, Sus=suspension	

Appendix I

30 Day Notice to Prior Authorize **Adcirca® (Tadalafil)**

Oklahoma Health Care Authority
May 2011

Manufacturer:	Eli Lilly & Co., Marketed by Lung Rx, LLC
Medical Classification:	Phosphodiesterase Type 5 (PDE-5) Inhibitor
FDA Status:	Prescription Only

Summary

Adcirca® (tadalafil) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Adcirca® reduces arterial hypertension by inhibition of phosphodiesterase type 5 (PDE5) which increases the concentrations of cGMP, resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed. Tadalafil is also marketed under the brand name Cialis®, which is indicated for the treatment of erectile dysfunction.

Adcirca® (tadalafil) is available as 20mg non-scored tablets indicated to be dosed once daily as one single dose of two 20mg tablets with or without food. Adcirca® is only available as 20mg tablets. Adcirca® is contraindicated in patients also using organic nitrates. Adcirca® interacts with medications metabolized via the cytochrome P450 system such as theophylline, warfarin, midazolam, lovastatin, etc. Patients taking potent inhibitors or inducers of CYP3A such as ritonavir, rifampin, ketoconazole, and itraconazole, should avoid using Adcirca®. Common and rare serious adverse effects along with warning and precautions are included in the product information.

The estimated acquisition cost (EAC) of Adcirca® is $20.50 per tablet ($41.00 per day), which is comparable to Revatio® (sildenafil) which has an EAC of $15.85 ($47.55 per day.)

Recommendations

The College of Pharmacy recommends prior authorization of Adcirca® with similar approval criteria to the Revatio®:

1. FDA approved diagnosis of pulmonary arterial hypertension.
2. Medical supervision by a pulmonary specialist and/or cardiologist.
3. Quantity limit of #60 tablets per 30 days will apply.

PRODUCT DETAILS OF ADCIRCA® (TADALAFIL)
FDA-APPROVED IN MAY 22, 2009

INDICATIONS: Adcirca® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

DOSAGE FORMS:
Adcirca® comes in a 20 mg, orange, film-coated, almond-shaped tablets (not scored) debossed with "4467".

ADMINISTRATION:
- Pulmonary Arterial Hypertension: The recommended dose of Adcirca® is 40 mg (two 20 mg tablets) taken with or without food. Dividing the dose (40 mg) over the course of the day is not recommended.
- Use with Ritonavir:
    - Coadministration of Adcirca® in Patients on Ritonavir
        - In patients receiving ritonavir for at least one week, start Adcirca® at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.
    - Coadministration of Ritonavir in Patients on Adcirca®
        - Avoid use of Adcirca® during the initiation of ritonavir. Stop Adcirca® at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume Adcirca® at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

CONTRAINDICATIONS:
- Concomitant Organic Nitrates: Do not use Adcirca® in patients who are using any form of organic nitrate, either regularly or intermittently. Adcirca® potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and Adcirca® on the nitric oxide/cGMP pathway.
- Hypersensitivity Reactions: Adcirca® is contraindicated in patients with a known serious hypersensitivity to tadalafil (Adcirca® or Cialis®). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

SPECIAL POPULATIONS:
- Pregnancy: Pregnancy Category B
- Nursing Mothers: It is not known whether tadalafil is excreted into human milk, caution should be exercised when Adcirca® is administered to a nursing woman.
- Pediatric Use: Safety and effectiveness of Adcirca® in pediatric patients have not been established.
- Renal Impairment:
    - Mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min): Start dosing at 20 mg once daily.
    - Severe (creatinine clearance <30 mL/min or on hemodialysis): Avoid use of Adcirca® because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.
- Hepatic Impairment:
    - Mild or moderate (Child Pugh Class A or B): Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once per day.
    - Severe (Child Pugh Class C): Patients with severe hepatic cirrhosis have not been studied. Avoid use of Adcirca®.
- Geriatric Patients: No dose adjustment is required in patients > 65 years of age without renal impairment or hepatic impairment.

WARNINGS & PRECAUTIONS:

- Cardiovascular Effects:
  - Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of Adcirca®. At least 48 hours should elapse after the last dose of Adcirca® before taking nitrates. If a patient has taken Adcirca® within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking Adcirca® should seek immediate medical attention.
  - PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing Adcirca®, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.
  - Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when Adcirca® is administered, the possibility of associated PVOD should be considered.
  - There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:
    - Patients with clinically significant aortic and mitral valve disease
    - Patients with pericardial constriction
    - Patients with restrictive or congestive cardiomyopathy
    - Patients with significant left ventricular dysfunction
    - Patients with life-threatening arrhythmias
    - Patients with symptomatic coronary artery disease
    - Patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension
  - Use with Alpha Blockers and Antihypertensives
    - PDE5 inhibitors, including Adcirca®, and alpha–adrenergic blocking agents are vasodilators with blood pressure–lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.
  - Use with Alcohol
    - Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.
- Effects on the Eye: Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

- Hearing Impairment: Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.
- Combination with Other PDE5 Inhibitors: Tadalafil is also marketed as Cialis®. The safety and efficacy of taking Adcirca® together with Cialis® or other PDE5 inhibitors have not been studied. Inform patients taking Adcirca® not to take Cialis® or other PDE5 inhibitors.
- Prolonged Erection: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. Adcirca® should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).
- Effects on Bleeding: PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. Adcirca ® has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although Adcirca ® has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS:

- headache
- gastrointestinal such as indigestion or nausea
- myalgia, backache
- nasopharyngitis, respiratory tract infections

DRUG INTERACTIONS:

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects.
- Potential for Pharmacodynamic Interactions with Adcirca®:
    - Nitrates: Do not use Adcirca® in patients who are using any form of organic nitrate
    - Alpha-blockers: PDE5 inhibitors, including Adcirca®, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated
    - Antihypertensives: PDE5 inhibitors, including Adcirca®, are mild systemic vasodilators. Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.
    - Alcohol: Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased.
- Potential for Other Drugs to Affect Adcirca®:
    - Ritonavir: Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.
    - Other Potent Inhibitors of CYP3A: Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of Adcirca®.
    - Potent Inducers of CYP3A: For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of Adcirca®.

- Potential for Adcirca® to Affect Other Drugs:
    - Cytochrome P450 Substrates: Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).
    - Aspirin: Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.
    - P-glycoprotein (e.g. digoxin): Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

PATIENT INFORMATION:

- Inform patients of contraindication of Adcirca® with any use of organic nitrates.
- Inform patients that tadalafil is also marketed as Cialis® for erectile dysfunction. Advise patients taking of Adcirca® not to take Cialis® or other PDE5 inhibitors.
- Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking of Adcirca®. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking of Adcirca®. These events may be accompanied by tinnitus and dizziness.

REFERENCES

Adcirca® Label Information. Eli Lilly and Company. Available online at: www.adcirca.com/pdf/Learn-about-Adcirca.pdf. Last revised February 8, 2011.

30 Day Notice to Prior Authorize Practitioner Administered Drugs, Including Benlysta® (belimumab)

Oklahoma Health Care Authority
May 2011

Manufacturer	Human Genome Sciences, Inc.
Classification	Monoclonal antibody
Status	Prescription Only

Summary

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder which may affect the skin, joints, kidney, and other organs. The specific mechanism of this disorder is not known. According to a recent report from the National Arthritis Data Working Group, approximately 250,000 Americans have SLE. The prevalence of SLE is highest among women aged 14-64 years. The presentation and course are highly variable, ranging from mild to potentially fatal. Joint pain is one of the most common reasons for the initial clinical presentation in patients with SLE, and may involve the hands, wrists, and knees. Cutaneous manifestations are common and include the "butterfly rash", an erythematous rash over the cheeks and nasal bridge; photosensitivity; discoid rash; and alopecia. The kidney is the most commonly involved visceral organ in SLE, although any organ system may be affected.

Treatment of systemic lupus erythematosus (SLE) depends on disease severity. Milder symptoms such as fever, rash, musculoskeletal manifestations, and serositis generally respond to treatment with hydroxychloroquine, NSAIDS, and low-to-moderate–dose corticosteroids, as necessary, for acute flares. Medications such as methotrexate may be useful in chronic lupus arthritis, and azathioprine and mycophenolate have been widely used in moderate severity lupus. CNS involvement and renal disease constitute more serious disease and often require high-dose steroids and other immunosuppressive agents such as cyclophosphamide, azathioprine, or mycophenolate. Class IV diffuse proliferative lupus nephritis has also been treated with aggressive cyclophosphamide induction therapy. Recent observational evidence suggests that hydroxychloroquine may have protective benefits in patients with SLE, including improved survival.

Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. Belimumab inhibits a B-lymphocyte stimulator (BLyS) protein, which leads to a decrease in the amount of abnormal B cells in the body. It is available as an intravenous infusion only, and is supplied as a 120 mg and 400 mg vial. The recommended dosage regimen is 10 mg/kg at 2 week intervals for the first 3 doses, and then it may be given every 4 weeks. The infusion is given over an hour but may be slowed if an infusion reaction occurs, and must be discontinued immediately if hypersensitivity develops. To prevent infusion and hypersensitivity reactions, it is advised that patients be premedicated with antihistamines.

Common adverse effects reported with belimumab include nausea, diarrhea, fever, infusion-site reactions, nasopharyngitis, bronchitis, insomnia, extremity pain, depression, migraine, and pharyngitis. A greater number of deaths and serious infections were reported in patients treated with belimumab than in those treated with placebo. It should be used with caution in patients with chronic infections, because serious and sometimes fatal infections have been reported in patients receiving belimumab or other immunosuppressive agents. Live vaccines should not be given during treatment with belimumab. Depression and suicidality have been reported

in clinical trials of belimumab, so patients should be monitored for new or worsening depression, suicidal thoughts, or other mood changes.

The safety and effectiveness of belimumab was demonstrated in 2 clinical trials that randomized a total of 1684 patients to receive either belimumab or placebo in combination with standard therapy. Treatment with belimumab plus standard therapy reduced disease activity and possibly decreased the number of severe flares and steroid use.

The current pricing for a 120 mg vial is $468, and for a 400 mg vial is $1,560. For a 70 kg patient, it is estimated the cost for a year of therapy with belimumab would be approximately $43,680. For the same 70 kg patient, estimated annual cost of therapy for cyclophosphamide is $2,538; azathioprine is $2,747; mycophenolate is $10,051; and hydroxychloroquine is $98.

Recommendations

The College of Pharmacy recommends medical prior authorization of Benlysta® (belimumab) for medical claims. In order to apply a consistent prior authorization policy to drug products supplied by either a pharmacy or practitioner's office, the College of Pharmacy recommends prior authorization of physician administered medications until these products can be formally reviewed by the DUR Board. The package labeling approved by the Food & Drug Administration (FDA) will be used as the interim criteria. Over the course of the next few months, several of these products will be presented and reviewed.

Benlysta® (belimumab) Approval Criteria:

1. FDA approved indication of adults with active, autoantibody-positive, systemic lupus erythematosus already receiving standard therapy.
2. Documented inadequate response to at least two of the following medications:
    a. High-dose oral corticosteroids
    b. Azathioprine
    c. Mycophenolate
    d. Cyclophosphamide
3. Prescription by rheumatologist only.
4. No combination use with biologic therapies or intravenous cyclophosphamide.

PRODUCT DETAILS OF BENLYSTA® (BELIMUMAB)

FDA-APPROVED IN MARCH 10, 2011

INDICATIONS: Benlysta® is indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

DOSAGE FORMS:

- Benlysta® is available in two strengths as single-use vials of belimumab lyophilized powder for injection:
  - 120 mg per vial
  - 400 mg per vial

ADMINISTRATION:

- Benlysta® is for intravenous infusion only and must be reconstituted and diluted prior to administration. Do not administer as an intravenous push or bolus.
- The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only, over a period of 1 hour. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a serious hypersensitivity reaction.
- Prior to dosing with Benlysta®, consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions.

CONTRAINDICATIONS:

- Benlysta® is contraindicated in patients who have had anaphylaxis with belimumab.

SPECIAL POPULATIONS:

- Pregnancy Category C: There are no adequate and well-controlled clinical studies using Benlysta® in pregnant women. Immunoglobulin G (IgG) antibodies, including Benlysta®, can cross the placenta. Because animal reproduction studies are not always predictive of human response, Benlysta® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should use adequate contraception during treatment with Benlysta® and for at least 4 months after the final treatment.
- Nursing Mothers: It is not known whether Benlysta® is excreted in human milk or absorbed systemically after ingestion. However, belimumab was excreted into the milk of cynomolgus monkeys. Because maternal antibodies are excreted in human breast milk, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of breastfeeding to the infant and the importance of the drug to the mother.
- Pediatric Use: Safety and effectiveness of Benlysta® have not been established in children.
- Geriatric Use: Clinical studies of Benlysta® did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Use with caution in elderly patients.
- Race: In Trial 2 and Trial 3, response rates for the primary endpoint were lower for black subjects in the Benlysta® group relative to black subjects in the placebo group. Use with caution in black/African-American patients.

WARNINGS & PRECAUTIONS:

- Mortality: There were more deaths reported with Benlysta® than with placebo during the controlled period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths occurred during the placebo-controlled, double-blind treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and

6/674 (0.9%) deaths in the placebo, Benlysta® 1 mg/kg, Benlysta® 4 mg/kg, and Benlysta® 10 mg/kg groups, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease and suicide.

- Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including Benlysta®. Physicians should exercise caution when considering the use of Benlysta® in patients with chronic infections. Patients receiving any therapy for chronic infection should not begin therapy with Benlysta®. Consider interrupting Benlysta® therapy in patients who develop a new infection while undergoing treatment with Benlysta® and monitor these patients closely
- Malignancy: The impact of treatment with Benlysta® on the development of malignancies is not known. As with other immunomodulating agents, the mechanism of action of Benlysta® could increase the risk for the development of malignancies.
- Hypersensitivity Reactions, Including Anaphylaxis:
    - Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea.
    - Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases. Some patients (13%) received premedication, which may have mitigated or masked a hypersensitivity response; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions.
    - Benlysta® should be administered by healthcare providers prepared to manage anaphylaxis. In the event of a serious reaction, administration of Benlysta® must be discontinued immediately and appropriate medical therapy administered.
    - Patients should be monitored during and for an appropriate period of time after administration of Benlysta®. Patients should be informed of the signs and symptoms of a hypersensitivity reaction and instructed to seek immediate medical care should a reaction occur.
- Infusion Reactions:
    - Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% of patients receiving Benlysta® and 0.4% of patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and hypotension.
    - The most common infusion reactions (≥ 3% of patients receiving Benlysta®) were headache, nausea, and skin reactions.
    - Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases. Some patients (13%) received premedication, which may have mitigated or masked an infusion reaction; however there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.
    - Benlysta® should be administered by healthcare providers prepared to manage infusion reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor patients closely.
- Depression:
    - Serious depression was reported in 0.4% (6/1458) of patients receiving Benlysta® and 0.1% (1/675) of patients receiving placebo.
    - Two suicides (0.1%) were reported in patients receiving Benlysta®.
    - The majority of patients who reported serious depression or suicidal behavior had a history of depression or other serious psychiatric disorders and most were receiving psychoactive medications. It is unknown if Benlysta® treatment is associated with increased risk for these events.

    - Patients receiving Benlysta® should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes.
- Immunization:
    - Live vaccines should not be given for 30 days before or concurrently with Benlysta® as clinical safety has not been established.
    - Because of its mechanism of action, Benlysta® may interfere with the response to immunizations.
- Concomitant Use with Other Biologic Therapies of Intravenous Cyclophosphamide: Benlysta® has not been studied in combination with other biologic therapies, including B-cell targeted therapies, or intravenous cyclophosphamide. Therefore, use of Benlysta® is not recommended in combination with biologic therapies or intravenous cyclophosphamide.

ADVERSE REACTIONS (≥3% of patients treated):

- Nausea
- Diarrhea
- Pyrexia
- Nasopharyngitis
- Bronchitis
- Insomnia
- Pain in extremity
- Depression
- Migraine
- Pharyngitis
- Cystitis
- Leukopenia
- Gastroenteritis viral

DRUG INTERACTIONS: Formal drug interaction studies have not been performed with Benlysta®. In clinical trials of patients with SLE, Benlysta® was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and NSAIDs without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated.

PATIENT INFORMATION: Patients should be given the Medication Guide for Benlysta® and provided an opportunity to read it prior to each treatment session. It is important that the patient's overall health be assessed at each infusion visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

- Patients should be advised that more patients receiving Benlysta® in the main clinical trials died than did patients receiving placebo treatment.
- Patients should be advised that Benlysta® may decrease their ability to fight infections. Patients should be asked if they have a history of chronic infections and if they are currently on any therapy for an infection. Patients should be instructed to tell their healthcare provider if they develop signs or symptoms of an infection.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, difficulty breathing, peri-oral or lingual edema, and rash. Patients should be instructed to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of Benlysta®.
- Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes.

- Patients should be informed that they should not receive live vaccines while taking Benlysta®. Response to vaccinations could be impaired by Benlysta®.
- Patients should be informed that Benlysta® has not been studied in pregnant women or nursing mothers so the effects of Benlysta® on pregnant women or nursing infants are not known. Patients should be instructed to tell their healthcare provider if they are pregnant, become pregnant, or are thinking about becoming pregnant. Patients should be instructed to tell their healthcare provider if they plan to breastfeed their infant.

REFERENCES

Benlysta® Label Information. GlaxoSmithKline, a subsidiary of Human Genome Sciences, Inc. Available online at: http://www.benlysta.com/?src=1&rotation=2056&banner=1854040&kw=5641400. Last revised March 2011.

30 Day Notice to Prior Authorize Colcrys® (Colchicine) and Uloric® (Febuxostat)

Oklahoma Health Care Authority
May 2011

Manufacturers: URL Pharma, Inc. and Takeda Pharmaceuticals North America, Inc.
Medical Classification: Antimitotic (colchicine) and Xanthine Oxidase Inhibitor (febuxostat)
FDA Status: Prescription Only

Colcrys® (Colchicine) Summary[1]

Colcrys® (colchicine) is indicated for prophylaxis and treatment of gout flares in adults, and Familial Mediterranean Fever (FMF) in adults and children 4 years or older. Colchicine is an old drug that has been on the market before the establishment of the Food and Drug Administration (FDA). On October 1, 2010, the FDA ordered all unapproved cholchicine products be removed from the market.[2] Colcrys® is a new extended release formulation of colchicine and is currently the only single-ingredient colchicine product on the market that is FDA approved. The combination products containing colchicine/probenecid manufactured by Watson Laboratories and Ivax Pharmaceuticals are still available on the market. The therapeutic ratio of benefits to adverse effects is usually poorer for colchicine than for other available oral treatments.

Colcrys® (colchicine) is available as 0.6mg tablets. For acute treatment, Colcrys® is taken as 1.2mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later. For prophylaxis, the dose is 0.6mg once or twice daily in adults and adolescents older than 16 years of age up to a maximum dose of 1.2 mg per day.

Uloric® (febuxostat) Summary[3]

Uloric® (febuxostat) is a new xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Allopurinol is currently the only other xanthine oxidase inhibitor on the market. Unlike allopurinol, Uloric® (febuxostat) is eliminated via both hepatic and renal pathways and does not require dosage reduction in patients with mild to moderate renal impairment.

Uloric® (febuxostat) is recommended at 40mg or 80mg once daily with or without food. The recommended starting dose of Uloric® is 40 mg once daily. For patients who do not achieve a serum uric acid less than 6mg/dL after 2 weeks with 40 mg, Uloric® 80mg is recommended. In comparative trials listed in the Uloric® label, Uloric® 80mg, but not the 40mg, was shown to be superior to allopurinol in lowering serum uric acid less than 6mg/dL. However, the allopurinol doses used in the trials ranged from 100mg to 300mg per day, which is listed as the minimal to average effective dose in allopurinol's medication label. The maximum recommended dose for allopurinol may be up to 800mg to 900mg per day.

Cost Comparison (January – March 2011)

CHEMICAL NAME	BRAND NAME	CLAIMS	UNITS	DAYS	MEMBERS	COST	UNITS/ DAY	COST/ DAY
Allopurinol	ALLOPURINOL TAB 100MG	407	20,829	14,747	233	$2,723.22	1.41	$0.18
Allopurinol	ALLOPURINOL TAB 300MG	485	22,679	21,327	309	$3,297.38	1.06	$0.15
Colchicine	COLCRYS TAB 0.6MG	59	2,408	1,432	40	$12,310.30	1.68	$8.60
Febuxostat	ULORIC TAB 40MG	40	1,186	1,186	19	$6,136.92	1	$5.17
Febuxostat	ULORIC TAB 80MG	19	555	570	11	$2,861.19	0.97	$5.02
Probenecid	PROBENECID TAB 500MG	19	1,260	543	8	$530.93	2.32	$0.98
Colchicine/Probenecid	PROBEN/COL TAB 500-0.5	2	120	120	2	$75.51	1	$0.63

Recommendations

The College of Pharmacy recommends prior authorization of Colcrys® (Colchicine) and Uloric® (febuxostat) with the following criteria:

Colcrys® (Colchicine) will have a free floating 2 days supply of 6 tablets per 365 days. Long term use of Colchicine will require a petition and member must have:

1. Failure of allopurinol defined by persistent gouty attacks with serum urate levels below 6.5mg/dL.
2. Clinical reason why colchicine/probenecid would not be a viable option for the member.
3. Members with the diagnosis of Familial Mediterranean Fever verified by genetic testing will be approved for up to 2.4mg per day.
4. Quantity limit of #60 per 30 days will apply.

Uloric® (febuxostat) approval criteria:

1. Failure of allopurinol defined by persistent gouty attacks with serum urate levels below 6.5mg/dL.
2. Clinical reason why allopurinol is not a viable option for the member.
3. Quantity limit of #30 per 30 days will apply.

PRODUCT DETAILS OF COLCRYS® (COLCHICINE)

INDICATIONS: Colcrys® is indicated for:

- Prophylaxis and treatment of gout flares in adults.
- Familial Mediterranean Fever (FMF) in adults and children 4 years or older.

DOSAGE FORMS:

- Colcrys® is available in one strength as a 0.6 mg tablet.

ADMINISTRATION:

- Gout Flares:
  - Prophylaxis: 0.6 mg once or twice daily in adults and adolescents older than 16 years of age. Maximum dose 1.2 mg/day.
  - Treatment: 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later.
- Familial Mediterranean Fever: Adults and children older than 12 years 1.2-2.4 mg; Children 6 to 12 years 0.9-1.8 mg; Children 4-6 years 0.3-1.8 mg.
  - Give total daily dose in one or two divided doses.
  - Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose.
- Colchicine tablets are administered orally, without regard to meals.

CONTRAINDICATIONS:

- Patients with renal or hepatic impairment should not be given Colcrys® in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicines toxicity has been reported with colchicine taken in therapeutic doses.

SPECIAL POPULATIONS:

- Pregnancy Category C: Use only if the potential benefit justifies the potential risk to the fetus.
- Nursing Mothers: Caution should be exercised when administered to a nursing woman.
- Geriatric Use: The recommended dose of colchicines should be based on renal function.
- Renal Impairment:
  - Mild to moderate: Adjustment of dosing is not required for treatment of gout flare, prophylaxis of gout flare, and FMF but patients should be monitored closely.
  - Severe:
    - Prophylaxis of gout flares: Starting dose of 0.3 mg/day
    - Treatment of gout flares: No dose adjustment is required but a treatment course should be repeated no more than once every 2 weeks.
    - FMF: Starting dose of 0.3 mg/day and any increase in dose should be done with close monitoring.
  - Patients undergoing dialysis:
    - Prophylaxis of gout flares: Total recommended dose should be 0.3 mg given twice a week with close monitoring.
    - Treatment of gout flares: Total recommended dose should be reduced to 0.6 mg (1 tablet) x 1 dose and the treatment course should not be repeated more than once every two weeks.
    - FMF: Starting dose of 0.3 mg/day and dosing can be increased with close monitoring.
- Hepatic Impairment:
  - Mild to moderate: Adjustment of dosing is not required for treatment of gout flare, prophylaxis of gout flare, and FMF but patients should be monitored closely.

- Severe: Dose reduction may be needed in prophylaxis of gout flares and FMF patients; while a dose reduction may not be needed in gout flares, a treatment course should be repeated no more than once ever y 2 weeks.

WARNINGS & PRECAUTIONS:

- Fatal Overdoses: Reported with colchicine in adults and children. Keep Colcrys® out of the reach of children.
- Blood Dyscrasias: Myelosuppression, leucopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported.
- Drug Interaction with P-gp and/or CYP3A Inhibitors: Co-administration of colchicine with P-gp and/or strong CYP3A4 inhibitors has resulted in life-threatening interactions and death.
- Monitor for toxicity and if present consider temporary interruption or discontinuation of colchicines.

ADVERSE REACTIONS (reported in ≥ 2% of patients treated):

- Diarrhea
- Nausea
- Vomiting
- Fatigue
- Gout
- Headache
- Pharyngolaryngeal pain

DRUG INTERACTIONS:

- Co-administration of P-gp and/or CYP3A4 inhibitors (e.g., clarithromycin or cyclosporine) have been demonstrated to alter the concentration of colchicines. The potential for drug-drug interactions must be considered prior to and during therapy.

PATIENT INFORMATION:

- Patients should be advised to keep Colcrys® out of the reach of children. Colcrys® can serious side effects or even death if levels are too high in the body.
- Patients should be advised to tell their healthcare provider about all of their medical conditions, including if they have kidney or liver problems.
- Certain medicines when taken with Colcrys® can cause the levels of colchicines to be too high in the body. It is important to advise patients to tell their healthcare provider about all the medicines they take, including prescription and non-prescription medicines, vitamins and herbal supplements. Colcrys® and other medicines may affect each other causing serious side effects or even death. Do not start taking a new medicine without telling your healthcare provider or pharmacist.
- Healthcare providers should emphasize to patients that even medications that they might take for a short period of time, such as antibiotics, can interact with Colcrys® and cause serious side effects or death.
- Patients should be advised to especially tell their healthcare provider if they take:
  - clarithromycin (Biaxin®)
  - telithromycin (Ketek®)
  - cyclosporine (Neoral®, Gengraf®, Sandimmune®)
  - ketoconazole (Nizoral®)
  - itraconazole (Sporanox®)
  - HIV protease inhibitors
  - nefazodone (Serzon®)
- Patients should be advised that Colcrys® is not a pain medicine and it should not be taken to treat pain related to other conditions unless specifically prescribed for those conditions.

PRODUCT DETAILS OF ULORIC® (FEBOXOSTAT)

INDICATIONS: Uloric® is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

DOSAGE and ADMINISTRATION:

- Uloric® is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6mg per dL after 2 weeks with 40 mg, Uloric® 80 mg is recommended.
- Uloric® can be administered without regard to food or antacid use.
- No dose adjustment is necessary when administering Uloric® to patients with mild to moderate renal or hepatic impairment.

CONTRAINDICATIONS: Patients being treated with azathioprine or mercaptopurine.

SPECIAL POPULATIONS:

- There is insufficient data in patients with severe renal impairment. No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients.
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, Uloric® is not recommended for use in these patients.

WARNINGS & PRECAUTIONS:

- Gout Flare: An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including Uloric®. If a gout flare occurs during treatment, Uloric® need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug (NSAID) or colchicine upon initiation of treatment) may be beneficial for up to six months.
- Cardiovascular Events: A higher rate of cardiovascular thromboembolic events was observed in patients treated with Uloric® than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke.
- Liver Enzyme Elevation: Transaminase elevations have been observed in Uloric® -treated patients. Monitor liver function tests periodically.

ADVERSE REACTIONS (reported in ≥ 2% of patients treated):

- liver function
- abnormalities
- nausea
- arthralgia
- rash

DRUG INTERACTIONS:

- Concomitant administration of Uloric® with XO substrate drugs, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity.
- Based on drug interaction studies in healthy subjects, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine

PATIENT INFORMATION:

- Before taking Uloric® tell your healthcare provider about all of your medical conditions, including:
    - liver or kidney problems
    - history of heart disease or stroke
    - pregnancy or plan to become pregnant; it is not known if Uloric® will harm your unborn baby.

- Talk with your healthcare provider if you are breast-feeding or plan to breast-feed. It is not known if Uloric® passes into your breast milk. You and your healthcare provider should decide if you should take Uloric® while breast-feeding.
- Your gout may flare up when you start taking Uloric®, do not stop taking your ULORIC even if you have a flare. Your healthcare provider may give you other medicines to help prevent your gout flares.
- Your healthcare provider may do certain tests while you take Uloric®.

[1] Colcrys® Label Information. URL Pharma, Inc. Available online at: http://www.colcrys.com/healthcare-professional/about-colcrys.htm. Last revised September 6, 2010.
[2] FDA News Release: FDA orders halt to marketing of unapproved single-ingredient oral colchicine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227796.htm
[3] Uloric® Label Information. Takeda Pharmaceuticals North America, Inc. Available at: http://www.uloricrx.com/

30 Day Notice to Prior Authorize Miscellaneous Bladder Agents

Oklahoma Health Care Authority
May 2011

Summary

Painful urination can be due to a number of causes, including but not limited to kidney stones or kidney infections, sexually transmitted diseases, prostatitis, urethritis, yeast infections, diagnostic procedures, or causes as simple as dehydration. There are a group of combination products indicated for the relief of local symptoms of irritative voiding. The chart below outlines the products that are currently covered by SoonerCare, their mechanisms of action, and comparative cost:

Name	Methenamine	Methylene Blue	Hyoscyamine	Sodium Phosphate	Salicylate	Benzoic Acid	Cost/ Tablet
Urelle®	X	X	X	X	X		$3.21
Prosed-DS®	X	X	X		X	X	$2.36
Darpaz®	X	X	X	X	X		$1.75
Urogesic Blue®	X	X	X	X			$0.62
Uroqid Acid #2®	X			X			$0.38
Utira-C®	X	X	X	X	X		$0.37
Utrona-C®	X	X	X	X	X		$0.37
Darcalma®	X	X	X	X	X		$0.37

Methenamine and methylene blue are antiseptic.
Salicylate is a pain reliever
Sodium phosphate acidifies the urine, aiding in the antiseptic effects.
Hyoscyamine is an antispasmodic.
Benzoic Acid is a topical antiseptic.

The dosing is usually one tablet orally 4 times per day followed by liberal fluid intake. Common adverse reactions include tachycardia, flushing, dizziness, nausea, acute urinary retention or difficult micturition, discoloration of urine (blue), blurred vision, and shortness of breath.

Recommendations

The College of Pharmacy recommends prior authorization of Urelle®, Prosed DS®, and Darpaz® with the following approval criteria:

1. Recent 14 day trials within the past 30-60 days of:
    a. Urogesic Blue®,
    b. Utira-C®, Utrona-C®, or Darcalma®

PRODUCT DETAILS OF URELLE® (HYOSCYAMINE SULFATE, METHENAMINE, METHYLENE BLUE, PHENYL SALICYLATE, SODIUM PHOSPHATE MONOBASIC)

INDICATIONS: Urelle® is indicated for three health problems:

- Treatment of symptoms of irritative voiding
- Relief of local symptoms, such as inflammation, hypermotility, and pain, which accompany lower urinary tract infections
- Relief of urinary tract symptoms caused by diagnostic procedures

DOSAGE FORMS:

- Urelle® is available as tablets for oral administration.

ADMINISTRATION:

- Adults: One tablet orally 4 times per day followed by liberal fluid intake
- Pediatric: Dosage must be individualized by a physician for older children. Urelle® is not recommended for use in children 6 years of age or younger.

CONTRAINDICATIONS:

- Hypersensitivity to any of the ingredients is possible. Risk-benefit should be carefully considered when the following medical problems exist: cardiac disease (especially cardiac arrthymias, congestive heart failure, coronary heart disease, mitral stenosis); gastrointestinal tract obstructive disease; glaucoma; myasthenia gravis; acute urinary retention may be precipitated in obstructive uropathy (such as bladder neck obstruction due to prostatic hypertrophy).

SPECIAL POPULATIONS:

- Pregnancy Category C
- Nursing Mothers: Enters breast milk so use caution if breastfeeding.
- Geriatric Population: Use with caution in the elderly due to the fact that they may be more sensitive to anticholinergic effects of hyoscyamine.
- Pediatric Population: Safety and efficacy have not been established in children ≤ 6 years of age.

WARNINGS & PRECAUTIONS:

- Belladonna alkaloid allergy: Use with caution in patients with a history of intolerance to belladonna alkaloids.
- Blurred vision: Discontinue use immediately if dizziness occurs.
- Salicylate allergy: Use with caution in patients with a history of intolerance to salicylates.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, C. difficile-associated diarrhea and pseudomembranous colitis.
- Tachycardia: Discontinue use immediately if tachycardia occurs.
- Use with caution in patients with cardiovascular disease, gastrointestinal tract obstruction, glaucoma, myasthenia gravis, and obstructive neuropathy.

ADVERSE REACTIONS (frequency not defined):

- Tachycardia
- Flushing
- Dizziness
- Nausea
- Vomiting
- Acute urinary retention
- Discoloration of urine (blue)

- Blurred vision
- Shortness of breath

DRUG INTERACTIONS:

- Allow at least 2 hours after ketoconazole. May be potentiated by antimuscarinics, antimyasthenics, MAOIs, opioids. May be antagonized by thiazide diuretics, urinary alkalinizers. Separate dosing of antacids, antidiarrheals by 1 hour. May reduce absorption of other drugs. Sulfonamides precipitate with formaldehyde in urine; avoid concomitant use.

PRODUCT DETAILS OF PROSED® DS (METHENAMINE, PHENYL SALICYLATE, METHYLENE BLUE, BENZOIC ACID, HYOSCYAMINE SULFATE)

INDICATIONS: Prosed® DS is indicated for the relief of discomfort of the lower urinary tract caused by hypermotility resulting from inflammation or diagnostic procedures and in the treatment of cystitis, urethritis and trigonitis when caused by organisms which maintain or produce an acid urine and are susceptible to formaldehyde.

DOSAGE FORMS:

- Prosed® DS is available as tablets for oral administration.

ADMINISTRATION:

- Adults: One tablet orally 4 times per day followed by liberal fluid intake.
- Older children: Dosage must be individualized by physician. Not recommended for use in children up to 12 years of age.

CONTRAINDICATIONS: Risk-benefit should be considered when the following medical problems exist:

- Glaucoma
- Urinary bladder neck obstruction
- Pyloric or duodenal obstruction or cardiospasm
- Hypersensitivity to any of the ingredients

SPECIAL POPULATIONS:

- Pregnancy Category C: Hyoscyamine and methenamine cross the placenta. Studies have not been done in either animals or humans. It is not known whether Prosed® DS tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Prosed® DS tablets should be given to a pregnant woman only if clearly needed.
- Nursing mothers: Methenamine and traces of hyoscyamine are excreted in breast milk. Caution should be exercised when Prosed® DS tablets are administered to nursing mothers.
- Pediatric: Infants and young children are especially susceptible to the toxic effect of the belladonna alkaloids.
- Geriatric: Use with caution in elderly patients as they may respond to the usual doses of the belladonna alkaloids with excitement, agitation, drowsiness, or confusion.

WARNINGS & PRECAUTIONS:

- Cross sensitivity and/or related problems: Patients intolerant of other belladonna alkaloids or other salicylates may be intolerant of this medication also. Delay in gastric emptying could complicate the management of gastric ulcers.
- Prolonged use: There have been no studies to establish the safety of prolonged use in humans. No known long-term animal studies have been performed to evaluate carcinogenic potential.

- Do not exceed recommended dosage. If rapid pulse, dizziness or blurring of vision occurs, discontinue use immediately.

ADVERSE REACTIONS (frequency not defined):
- Cardiovascular: rapid pulse, flushing
- CNS: blurred vision, dizziness
- Respiratory: shortness of breath or troubled breathing
- Genitourinary: difficult micturition, acute urinary retention, blue-green colored urine
- Gastrointestinal: dry mouth, nausea/vomiting

DRUG INTERACTIONS: As a result of hyoscyamine's effects on gastrointestinal motility and gastric emptying, absorption of other oral medications may be decreased during concurrent use with this combination medication.
- Urinary alkalizers and thiazide diuretics: may cause the urine to become alkaline reducing the effectiveness of methenamine by inhibiting its conversion to formaldehyde.
- Antimuscarinics: Concurrent use may intensify antimuscarinic effects of hyoscyamine because of secondary antimuscarinic activities of these medications.
- Antacids/antidiarrheals: Concurrent use may intensify antimuscarinic effects of hyoscyamine resulting in decreased therapeutic effectiveness. Concurrent use with antacids may cause urine to become alkaline reducing the effectiveness of methenamine by inhibiting its conversion to formaldehyde. Doses of these medications should be spaced 1 hour apart from doses of hyoscyamine.
- Antimyasthenics: Concurrent use with hyoscyamine may further reduce intestinal motility, therefore, caution is recommended.
- Ketoconazole: May cause increased gastrointestinal pH. Concurrent administration with hyoscyamine may result in marked reduction in the absorption of ketoconazole. Patients should be advised to take this combination at least 2 hours after ketoconazole.
- Monoamine oxidase (MAO) inhibitors: Concurrent use with hyoscyamine may intensify antimuscarinic side effects.
- Opoid (narcotic) analgesics: May result in increased risk of severe constipation.
- Sulfonamides: These drugs may precipitate with formaldehyde in the urine increasing the danger of crystalluria.

PRODUCT DETAILS OF DARPAZ (HYOSCYAMINE SULFATE, METHENAMINE, METHYLENE BLUE, PHENYL SALICYLATE, SODIUM PHOSPHATE MONOBASIC)

INDICATIONS: Darpaz is indicated for three health problems:
- Treatment of symptoms of irritative voiding
- Relief of local symptoms, such as inflammation, hypermotility, and pain, which accompany lower urinary tract infections
- Relief of urinary tract symptoms caused by diagnostic procedures

DOSAGE FORMS:
- Darpaz is available as tablets for oral administration.
- Hyoscyamine sulfate 0.12 mg; methenamine 81 mg; methylene blue 10.8 mg; phenyl salicylate 32.4 mg; sodium phosphate monobasic 40.8mg

ADMINISTRATION:
- Adults: One tablet orally 4 times per day, followed by liberal fluid intake

- Pediatric: Dosage must be individualized by a physician for older children. Darpaz is not recommended for use in children younger than 6 years.

CONTRAINDICATIONS:

- Hypersensitivity to any of its ingredients. Risk-benefit should be carefully considered when the following medical problems exist: achalasia of esophagus, atony of colon, diseases of cardiovascular system, gastrointestinal hemorrhage; glaucoma; hemolytic anemia from pyruvate kinase and G6PD defiencies, infected urolithiasis, myasthenia gravis, paralytic ileus, severe ulcerative colitis, toxic megacolon; acute urinary retention may be precipitated in obstructive uropathy (such as bladder neck obstruction due to prostatic hypertrophy).

SPECIAL POPULATIONS:

- Pregnancy Category C: Hyoscyamine sulfate and methenamine cross the placenta.
- Nursing Mothers: Enters breast milk so use caution if breastfeeding.
- Geriatric Population: Use with caution in the elderly as they may respond to usual doses of hyoscyamine sulfate with excitement, agitation, drowsiness or confusion.
- Pediatric Population: Safety and efficacy have not been established in children ≤ 6 years of age.

WARNINGS & PRECAUTIONS:

- Cross sensitivity: Patients intolerant of belladonna alkaloids or salicylates may be intolerant of this medication also.
- Blurred vision: May cause dizzy, drowsy, or blurred vision; use caution while driving, using machinery, or doing any activity that requires alertness or clear vision.
- Delay in gastric emptying could complicate the management of gastric ulcers.

ADVERSE REACTIONS (frequency not defined):

- Cardiovascular: rapid heartbeat, flushing
- CNS: blurred vision, dizziness, drowsiness
- Genitourinary: difficulty micturition, acute urinary retention
- Respiratory: shortness of breath or trouble breathing
- Urine/stools to turn blue-green in color

DRUG INTERACTIONS:

- This drug should not be used with the following medications because very serious interactions may occur: live influenza virus vaccine, pramlintide.
- Doses of urinary alkalizers, thiazide diuretics, antimuscarinics, antacids/antidiarrheals should be spaced 1 hour apart from doses of hyoscyamine to avoid a decrease in absorption. Patients should be advised to take Darpaz at least 2 hours after ketoconazole dose.

REFERENCES

Prosed® DS Label Information. Ferring Pharmaceuticals, Inc. Available online at: http://www.prosed.com//. Accessed April 20, 2011.
Urelle® Label Information. Azur Pharma, Inc. Available online at: http://www.empr.com/urinary-tract-disorders/urelle/drug/6920/.
Darpaz® Label Information. River's Edge Pharmaceuticals, Inc. Available online at: http://www.drugs.com/pro/darpaz.html

30 Day Notice to Prior Authorize Neudexta™ (dextromethorphan/quinidine)

Oklahoma Health Care Authority
May 2011

Manufacturer: Avanir Pharmaceuticals, Inc.
Medical Classification: Not Current Classification
FDA Status: Prescription Only

Summary[1]

Nuedexta™ is indicated for the treatment of pseudobulbar affect (PBA), also called pathological laughing and crying, affective lability, emotional dyscontrol, emotional incontinence, and involuntary emotional expression disorder, in patients with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Nuedexta™ is a combination of dextromethorphan hydrobromide 20mg and quinidine sulfate 10mg. Dextromethorphan is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and a sigma-1 receptor agonist with an unknown mechanism of therapeutic effectiveness in pseudobulbar affect. Quinidine competitively inhibits the metabolism of dextromethorphan by CYP2D6, thereby increasing and prolonging plasma levels of dextromethorphan.

Nuedexta™ is indicated to be dosed once daily for 7 days, then twice daily therafter. Nuedexta™ can be taken with or without food. The patient should be assessed periodically to determine if continued use is necessary.

The efficacy of Nuedexta™ was demonstrated in a randomized double blind, placebo controlled, multicenter trial totaling 326 patients.[2] The trial compared two different doses of the dextromethorphan/quinidine combination, given twice daily, vs. placebo, given twice daily, for 12 weeks. Although daily PBA episodes decreased in all groups, the daily rate of PBA episodes was 47% lower for patients taking dextromethorphan/ quinidine 30mg/10mg, and 49% lower with dextromethorphan/quinidine 20mg/10mg compared with placebo (both $P < .001$). The mean decrease in the number of daily PBA episodes was 3.9 to 4.1 with active treatment and 3.0 with placebo.

Nuedexta™ is contraindicated in patients with prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, heart failure, or patients taking monoamine oxidase inhibitors (MAOIs), patients who are allergice to quinidine, mefloquine, or dextromethorphan. Diarrhea, flatulence, and dizziness are the most commonly reported adverse effects. Other serious adverse effects, mostly related to the use of quinidine, are included in the product information section.

The estimated acquisition cost (EAC) of Nuedexta™ is $8.61 per tablet ($17.22 per day), which makes Nuedexta™ therapy $516 per month.

Recommendations

The College of Pharmacy recommends prior authorization of Nuedexta™ with the following approval criteria:

1. FDA approved diagnosis of pseudobulbar affect due to amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS).
2. Member must be 18 years of age or older.
3. Quantity limit of #60 tablets per 30 days will apply.
4. Approval will be for 90 day intervals to ensure periodic assessment and determination that continued use is necessary.

PRODUCT DETAILS OF NUEDEXTA™ (DEXTROMETHORPHAN/QUINIDINE)

FDA-APPROVED IN OCTOBER 2010

INDICATIONS: Nuedexta™ is indicated for the treatment of pseudobulbar affect (PBA) in patients with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS).

DOSAGE FORMS:

- Nuedexta™ is an oral capsule that is available in one strength
- dextromethorphan hydrobromide 20 mg and quinidine sulfate 10 mg

ADMINISTRATION:

- For oral administration only with or without food.
- Administer twice-daily doses every 12 hours.
- Adults: One capsule daily for 7 days, then increase to one capsule twice daily.
- Reassess patient periodically to determine if continued use is necessary.

CONTRAINDICATIONS:

- Concomitant use with **quinidine, quinine, or mefloquine**.
- **Hypersensitivity**: Patients with a history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reaction. Also contraindicated in patients with known hypersensitivity to dextromethorphan.
- **MAOIs**: Use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping Nuedexta™ before starting an MAOI.
- **Cardiovascular**: Contraindicated in patients with prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure. Also patients with complete atrioventricular (AV) block without implanted pacemaker, or patients at high risk of complete AV block. Nuedexta is also contraindicated in patients receiving concomitant use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide).

SPECIAL POPULATIONS:

- **Pregnancy Category C**: Based on animal data, may cause fetal harm.
- **Nursing Mothers:** It is not known whether Nuedexta™ is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nuedexta™ is administered to a nursing woman.
- **Pediatric Use:** The safety and effectiveness of Nuedexta™ in pediatric patients below the age of 18 have not been established.
- **Geriatric Use:** Clinical study of Nuedexta™ did not include sufficient number of patients aged 65 and over to determine if dosage change in geriatric patients is warranted.
- **Renal Impairment**: Dose adjustment is not required in patients with mild to moderate renal impairment. The pharmacokinetics of Nuedexta™ have not been evaluated in patients with severe renal impairment; however, increases in dextromethorphan and/or quinidine levels are likely to be observed.
- **Hepatic Impairment:** Dose adjustment is not required in patients with mild to moderate hepatic impairment. The pharmacokinetics of Nuedexta™ have not been evaluated in patients with severe hepatic impairment; however, increases in dextromethorphan and/or quinidine levels are likely to be observed.

WARNINGS & PRECAUTIONS:

- **Thrombocytopenia and Other Hypersensitivity Reactions**: Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. Nuedexta™ should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is clearly not drug-

related, as continued use increases the risk for fatal hemorrhage. Likewise, Nuedexta™ should not be restarted in sensitized patients, because more rapid and more severe thrombocytopenia than the original episode can occur. Nuedexta™ should not be used if immune-mediated thrombocytopenia from structurally related drugs including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually, but not always, resolves within a few days of discontinuation of the sensitizing drug. Quinidine has also been associated with a lupus-like syndrome involving polyarthritis, sometimes with a positive antinuclear antibody test. Other associations include rash, bronchospasm, lymphadenopathy, hemolytic anemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevation in serum levels of skeletal-muscle enzymes, and pneumonitis.

- **Hepatotoxicity**: Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Fever may be a presenting symptom, and thrombocytopenia or other signs of hypersensitivity may also occur. Most cases remit when quinidine is withdrawn.
- **Cardiac Effects**: Nuedexta™ causes dose-dependent QTc prolongation. QT prolongation can cause torsades de pointes-type ventricular tachycardia, with the risk increasing as the degree of prolongation increases. When initiating Nuedexta™ in patients at risk of QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation of QT interval should be conducted at baseline and 3-4 hours after the first dose. This includes patients concomitantly taking/initiating drugs that prolong the QT interval or that are strong or moderate CYP3A4 inhibitors, and patients with left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease, or history of stroke. LVH and LVD can be diagnosed utilizing echocardiography or another suitable cardiac imaging modality.
- **Concomitant use of CYP2D6 Substrates**: The quinidine in Nuedexta™ inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with Nuedexta™ that are metabolized by CYP2D6.
- **Dizziness**: Nuedexta™ may cause dizziness. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls.
- **Serotonin Syndrome**: When used with SSRI's (such as fluoxetine) or tricyclic antidepressants (such as clomipramine and imipramine), Nuedexta™ may cause "serotonin syndrome", with changes included altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyper-reflexia, diaphoresis, shivering, and tremor.
- **Anticholinergic Effects of Quinidine**: Monitor for worsening clinical condition in myasthenia gravis and other conditions that may be adversely affected by anticholinergic effects.
- **CYP2D6 Poor Metabolizers**: The quinidine component of Nuedexta™ is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of Nuedexta™ is not expected to contribute to the effectiveness of Nuedexta™ in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with Nuedexta™. Caution should be exercised.

ADVERSE REACTIONS:

- Gastrointestinal: Diarrhea (13%), vomiting (5%), flatulence (3%)
- Central nervous system: Dizziness (10%)

DRUG INTERACTIONS:

- **MAOIs:** Do not use Nuedexta™ with monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days.
- **Drugs that Prolong QT and are Metabolized by CYP2D6**: Do not use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide).
- **Drugs that Prolong QT and Concomitant CYP3A4 Inhibitors**: Recommend ECG in patients taking drugs with Nuedexta™ that prolong the QT interval and in patients taking concomitant moderate or strong CYP3A4 inhibitors.
- **SSRIs and Tricyclic Antidepressants**: Use of Nuedexta™ with SSRIs or tricyclic antidepressants increases the risk of serotonin syndrome
- **CYP2D6 Substrate**: The co-administration of Nuedexta™ with drugs that undergo extensive CYP2D6 metabolism may result in altered drug effects, due to accumulation of parent drug and/or failure of metabolite formation. Therapy with medications that are primarily metabolized by CYP2D6 and that have a relatively narrow therapeutic index should be initiated at a low dose if a patient is receiving Nuedexta™ concurrently. If Nuedexta™ is added to the treatment regimen of a patient already receiving a drug primarily metabolized by CYP2D6, the need for a dose modification of the original medication should be considered. The extent to which CYP2D6 interactions may pose clinical problems will depend on the pharmacokinetics of the substrate involved.
- **Digoxin:** Quinidine is an inhibitor of P-glycoprotein. Concomitant administration of quinidine with digoxin, a P-glycoprotein substrate, results in serum digoxin levels that may be as much as doubled. Plasma digoxin concentrations should be closely monitored in patients taking Nuedexta™ concomitantly, and the digoxin dose reduced, as necessary.
- **Alcohol:** As with any other CNS drug, caution should be used when Nuedexta™ is taken in combination with other centrally acting drugs and alcohol.

PATIENT INFORMATION:

- Patients should be advised to take Nuedexta™ exactly as prescribed. Instruct patient not to take more than 2 capsules in a 24-hour period and to make sure there is an appropriate 12-hour interval between doses, and not to take a double dose after they miss a dose.
- Advise patients that Nuedexta™ may cause dizziness.
- Advise patients to consult their healthcare provider immediately if they feel faint or lose consciousness.
- Counsel patients on the risks associated with Nuedexta™.

[1] **Nuedexta™ Label Information.** Avanir™ Pharmaceuticals, Inc,. Available online at: www.**nuedexta**.com/**NUEDEXTA**_Full_Prescribing_Information-1.pdf. Last revised October 2010.

[2] Kaye R, Pratt C. **Summary of cardiac safety from a randomized, placebo-controlled, trial of dextromethorphan/ quinidine (STAR) for treatment of pseudobulbar affect.** Paper presented at: Annual Meeting of the American Academy of Neurology; April 15, 2010; Toronto, Ontario, Canada.

30 Day Notice to Prior Authorize Testosterone Replacement Products

Oklahoma Health Care Authority
May 2011

Summary

Testosterone products are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone:

1. Primary hypogonadism (congenital or acquired) – testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchidectomy.
2. Hypogonadotropic hypogonadism (congenital or acquired) – idiopathic gonadotropin or luteinizing-hormone-releasing hormone (LHRH) deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation. If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.
3. Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty.
4. Androgens may be used secondarily in women with advancing inoperable metastatic mammary cancer who are 1 to 5 years postmenopausal, or premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor.

Currently, there are five formulations of testosterone replacement products:

Buccal	Testosterone (Striant®)
Powder	Methyltestosterone Powder
Oral	Fluoxymesterone (Androxy® Tab) Methyltestosterone (Testred® Cap, Android® Cap, Methitest® Tab)
Intramuscular Injection	Testosterone Cypionate (Depo-Testosterone®) Testosterone Enanthate (Delatestryl®)
Transdermal	Testosterone Patch (Androderm®) Testosterone Topical Gel (Androgel®, Testim®, Fortesta®, Axiron®)

Oral agents are not recommended due to extensive metabolism of the drug by the liver, leading to a very small amount of hormone entering the circulation. The first pass absorption of oral agents through the liver causes the highest degree of toxicity of all the replacement therapy options. These include lowering of high-density lipoprotein (HDL) cholesterol and liver toxicity.[1]

Injectable agents are more often used for replacement therapy. The depot injections are given intramuscularly, usually dosed every 2-3 weeks. There may be an initial peak in testosterone level right after an injection, leading to adverse effects, or a drop of the testosterone level below the normal range shortly before the next injection, leading to increased symptoms. Slight titration of the dose or the dosing interval may resolve this issue.

The use of topical agents is thought to minimize adverse events to the user.[2] Recent warnings highlight the risk of secondary exposure to women and children coming into contact with the application sight and/or from residual drug left on the hands after application.[3]

General Contraindications:

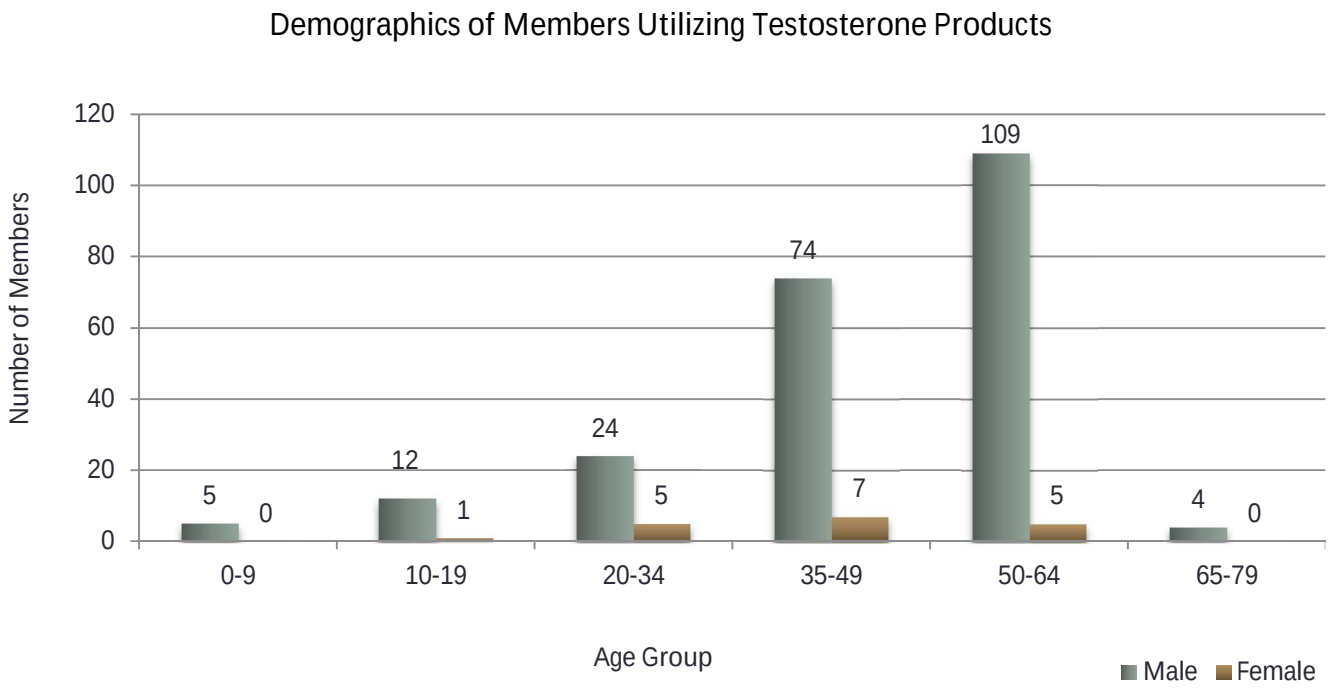
1. Known hypersensitivity to the drug
2. Males with carcinoma of the breast
3. Males with known or suspected carcinoma of the prostate gland
4. Women who are or who may become pregnant
5. Patients with serious cardiac, hepatic or renal disease

General Warnings and Precautions:

- Risk of secondary exposure with topical formulations
- Edema with or without congestive heart failure (CHF) may be a complication in patients with pre-existing cardiac, renal, or hepatic disease
- Hypercalcemia in immobilized patients
- Gynecomastia
- Alteration of serum lipid profile (raise low-density lipoproteins, lower high-density lipoprotein, and raise triglycerides)
- Sleep apnea may occur in those with risk factors
- Worsening symtoms of benign prostatic hyperplasia (BPH)
- Impairment of Spermatogenesis
- Liver toxicity

Utilization of Testosterone Products (January – March 2011)

CHEMICAL NAME	BRAND NAME	CLAIMS	MEMBERS	COST	COST/ DAY	% COST	COST/ CLAIM
Testosterone Enanthate	TESTOST ENAN INJ 200MG/ML	15	13	$912.46	$0.77	1.21%	$60.83
Testosterone Cypionate	DEPO-TESTOST INJ 200MG/ML	15	10	$910.21	$1.58	1.21%	$60.68
Testosterone Cypionate	TESTOST CYP INJ 200MG/ML	101	82	$8,015.92	$1.19	10.66%	$79.37
Testosterone Cypionate	DEPO-TESTOST INJ 100MG/ML	4	4	$336.48	$1.16	0.45%	$84.12
Testosterone Cypionate	TESTOST CYP INJ 100MG/ML	23	18	$1,023.00	$0.58	1.36%	$44.48
Testosterone Patch	ANDRODERM DIS 5MG/24HR	9	4	$3,428.70	$12.70	4.56%	$380.97
Testosterone Patch	ANDRODERM DIS 2.5MG/24	8	5	$1,980.38	$7.33	2.63%	$247.55
Testosterone Gel	FORTESTA GEL 10MG/ACT	1	1	$258.80	$8.63	0.34%	$258.80
Testosterone Gel	ANDROGEL GEL PUMP 1%	71	47	$21,458.77	$10.52	28.53%	$302.24
Testosterone Gel	TESTIM GEL 1%(50MG)	41	25	$13,756.78	$11.46	18.29%	$335.53
Testosterone Gel	ANDROGEL GEL 1%(50MG)	51	32	$15,503.84	$10.27	20.61%	$304.00
Testosterone Gel	ANDROGEL GEL 1%(25MG)	5	2	$1,419.49	$9.46	1.89%	$283.90
Testosterone Powder	TESTOSTERONE POW	2	2	$7.31	$0.06	0.01%	$3.66
Methyltestosterone Pow	METHYLTESTOS POW	2	1	$7.84	$0.13	0.01%	$3.92
Methyltestosterone	METHITEST TAB 10MG	1	1	$161.84	$1.62	0.22%	$161.84
Methyltestosterone	ANDROID CAP 10MG	1	1	$318.06	$10.60	0.42%	$318.06
Methyltestosterone	TESTRED CAP 10MG	7	3	$4,352.90	$20.73	5.79%	$621.84
Fluoxymesterone	ANDROXY TAB 10MG	3	1	$1,357.56	$15.08	1.81%	$452.52
	TOTAL	360	244	$75,210.34	$4.53	100.00%	$208.90



Recommendations

The College of Pharmacy recommends prior authorization of all testosterone products to ensure safe and appropriate use. The following is the recommended approval criteria:

1. FDA approved indication (must include lab showing pre-medication testosterone level below 249ng/dl).
2. Oral agents are only approved in cases where member cannot use all other available formulations of testosterone.

[1] Dana A. Ohl; Susanne A. Quallich. Clinical Hypogonadism and Androgen Replacement Therapy: An Overvie. Urol Nurs. 2006;26(4):253-259,269Nurs. 2006;26(4):253-259,269. Available online at: http://www.medscape.com/viewarticle/543997_print

[2] Steidle, C., Schwartz, S., Jacoby, K., Sebree, T., Smith, T., Bachand, R., et al. testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. Journal of Clinical Endocrinology & Metabolism, 88(6), 2673-2681.

[3] FDA Drug Safety Newsletter. 2009. Available online at: http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm189806.htm

Appendix J

U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: April 28, 2011
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Zytiga for late-stage prostate cancer

The U.S. Food and Drug Administration today approved Zytiga (abiraterone acetate) in combination with prednisone (a steroid) to treat patients with late-stage (metastatic) castration-resistant prostate cancer who have received prior docetaxel (chemotherapy).

In prostate cancer, the male sex hormone testosterone stimulates prostate tumors to grow. Drugs or surgery are used to reduce testosterone production or to block testosterone ŝ effects. However, sometimes prostate cancer can continue to grow even when testosterone levels are low. Men with these cancers are said to have castration-resistant prostate cancer.

Zytiga is a pill that targets a protein called cytochrome P450 17A1 (CYP17A1) which plays an important role in the production of testosterone. The dru works by decreasing the production of this hormone that would stimulate cancer cells to continue growing.

The application was reviewed under the FDA ŝ priority review program, which provides for an expedited six-month review for drugs that may offer major advances in treatment, or provide a treatment when no adequate therapy exists. Zytiga is being approved ahead of the product ŝ June 20, 2011 regulatory goal date.

"Zytiga prolonged the lives of men with late-stage prostate cancer who had received prior treatments and had few available therapeutic options, "said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA ŝ Center for Drug Evaluation and Research.

Zytiga ŝ safety and effectiveness were established in a clinical study of 1,195 patients with late-stage castration-resistant prostate cancer who had received prior treatment with docetaxel chemotherapy. Patients received either Zytiga once daily in combination with prednisone two times a day or a placebo (sugar pill) twice daily in combination with prednisone.

The study was designed to measure overall survival, the length of time from when the treatment started until a patient's death. Patients who received the Zytiga and prednisone combination had a median overall survival of 14.8 months compared to 10.9 months for patients receiving the placebo and prednisone combination.

The most commonly reported side effects in patients receiving Zytiga included joint swelling or discomfort, low levels of potassium in the blood, fluid retention (usually of the legs and feet), muscle discomfort, hot flashes, diarrhea, urinary tract infection, cough, high blood pressure, heartbeat disorders, urinary frequency, increased nighttime urination, upset stomach or indigestion and upper respiratory tract infection.

Zytiga is marketed by Horsham, Pa.-based Centocor Ortho Biotech, Inc.

For more information:

FDA: Office of Oncology Drug Products [1]

FDA: Approved Drugs: Questions and Answers [2]

NCI: Prostate Cancer [3]

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation ŝ food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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U.S. Food and Drug Administration

For Consumers

FDA Acts to Reduce Harm from Opioid Drugs

On This Page:

The White House on Tuesday unveiled a multi-agency plan aimed at reducing the "epidemic" of prescription drug abuse in the U.S.—including an FDA-backed education program that zeros-in on reducing the misuse and misprescribing of opioids.

Gil Kerlikowske, director of the White House Office of National Drug Control Policy, says the plan—a collaborative effort involving agencies of the departments of Justice, Health and Human Services, Veterans Affairs, Defense, and others—provides a national framework for reducing prescription drug abuse and the diversion of prescription drugs for recreational use.

"The toll our nation's prescription drug abuse epidemic has taken in communities nationwide is devastating," says Kerlikowske. "We share a responsibility to protect our communities from the damage done by prescription drug abuse."

Key elements of the plan—called Epidemic: Responding to America's Prescription Drug Abuse Crisis—include:

- expansion of state-based prescription drug monitoring programs
- recommending convenient and environmentally responsible ways to remove unused medications from homes
- supporting education for patients and health care providers
- reducing the number of "pill mills" and doctor-shopping through law enforcement

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FDA Opioid Strategy

In concert with the White House plan, the Food and Drug Administration (FDA) is announcing a new risk reduction program—called a Risk Evaluation and Mitigation Strategy—for all extended-release and long-acting opioid medications.

Opioids are synthetic versions of opium that are used to treat moderate and severe pain.

FDA experts say extended-release and long-acting opioids—including OxyContin, Avinza, Dolophine, Duragesic, and eight other brand names—are extensively misprescribed, misused, and abused, leading to overdoses, addiction, and even deaths across the United States. FDA says a 2007 survey revealed that more than half of opioid abusers got the drug from a friend or relative.

Opioids—such as morphine and oxycodone—are used to treat moderate and severe pain. Over the past few decades, drug makers have developed extended-release opioid formulas to treat people in pain over a long period.

The new REMS plan focuses primarily on: educating doctors about proper pain management, patient selection and other requirements and improving patient awareness about how to use these drugs safely. As part of the plan, FDA wants companies to give patients education materials, including a medication guide that uses consumer friendly language to explain safe use and disposal.

FDA wants drug makers to work together to develop a single system for implementing the REMS strategies. Toward that goal, FDA is now notifying opioid makers that they must propose a REMS plan within 120 days.

Janet Woodcock, director of FDA ś Center for Drug Evaluation and Research, says this risk management strategy is designed to improve pain management, while preserving patient access to these needed medications.

"This will be an important step toward addressing what has become a critical public health problem, "she says

Doctor training, patient counseling, and other risk reduction measures developed by opioid makers as part of the REMS are expected to become effective by early 2012. They will be required for various brand name products known under the generic names:

- hydromorphone
- oxycodone
- morphine
- oxymorphone
- methadone
- transdermal fentanyl
- transdermal buprenorphine

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Widespread Problem

FDA estimates that more than 33 million Americans age 12 and older misused extended-release and long-acting opioids during 2007—up from 29 million just five years earlier. And in 2006, nearly 50,000 emergency room visits were related to opioids.

"Opioid drugs have benefit when used properly and are a necessary component of pain management for certain patients, but we know that they pose serious risks when used improperly—with serious negative consequences for individuals, families, and communities," says FDA Commissioner Margaret A. Hamburg, M.D "The prescriber education component of this Opioid REMS balances the need for continued access to these medications with stronger measures to reduce their risks."

Although doctor training is not mandatory under the REMS plan, other federal agencies are working to get Congress to link mandatory physician training to the already required Drug Enforcement Administration registration number that doctors must have to prescribe controlled substances.

FDA will also require the risk management plan to include a way to determine if the education programs are helping to reduce problems associated with long-acting and extended-release opioids, as well as allowing patients who need opioids to get them.

FDA has had the power to request companies to develop REMS since 2007. The plans may also include medication guides and patient package inserts.

This article appears on FDA's Consumer Updates page[4], which features the latest on all FDA-regulated products.

April 19, 2011

For More Information

- Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS)[5]
- List of Long-Acting and Extended-Release Opioid Products Required to have an Opioid REMS[6]
- Questions and Answers: FDA Requires a Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids[7]

Related Consumer Updates

- Combating Misuse and Abuse of Prescription Drugs: Q&A with Michael Klein, Ph.D.[8]

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U.S. Food and Drug Administration

Drugs

List of Long-Acting and Extended-Release Opioid Products Required to have an Opioid REMS

Brand Name Products

	Trade Name	Generic Name	Sponsor
1	Duragesic	Fentanyl Transdermal System	Ortho McNeill Janssen
2	*Palladone	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma
3	Dolophine	Methadone hydrochloride tablets	Roxanne
4	Avinza	Morphine sulfate extended-release capsules	King Pharms
5	Kadian Capsules	Morphine sulfate extended-release capsules	Actavis
6	MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma
7	Oramorph	Morphine sulfate sustained-release tablets	Xanodyne Pharms
8	*Embeda	Morphine sulfate and naltrexone extended-release capsules	King Pharms
9	OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma
10	Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharma
11	Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt
12	Butrans	Buprenorphine Transdermal System	Purdue Pharma

*No longer being marketed, but is still approved.

Generic Products

	Drug Name	Generic Name	Sponsor
1	Fentanyl	Fentanyl extended-release transdermal system	Actavis
2	Fentanyl	Fentanyl extended-release transdermal system	Lavipharm Labs
3	Fentanyl	Fentanyl extended-release transdermal system	Mallinckrodt
4	Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies
5	Fentanyl	Fentanyl extended-release transdermal system	Noven
6	Fentanyl	Fentanyl extended-release transdermal system	Teva Pharms
7	Fentanyl	Fentanyl extended-release transdermal system	Watson
8	Methadone	Methadone tablets	Mallinckrodt
9	Methadone	Methadone HCL tablets	Mallinckrodt
10	Methadone	Methadone HCL tablets	Sandoz
11	Morphine	Morphine sulfate extended-release tablets	Endo
12	Morphine	Morphine sulfate extended-release tablets	KV Pharmaceuticals
13	Morphine	Morphine sulfate extended-release tablets	Mallinckrodt
14	Morphine	Morphine sulfate extended-release tablets	Watson Labs
15	Oxycodone	**Oxycodone extended-release tablets	Mallinckrodt
16	Oxycodone	** Oxycodone Extended-Release Tablets	Impax Labs
17	Oxycodone	** Oxycodone Extended-Release Tablets	Teva

** Discontinued products

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U.S. Food and Drug Administration

News & Events

FDA NEWS RELEASE

For Immediate Release: May 2, 2011
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Consumer Inquiries: 888-INFO-FDA

FDA approves new treatment for Type 2 diabetes

The U.S. Food and Drug Administration today approved Tradjenta (linagliptin) tablets, used with diet and exercise, to improve blood glucose control in adults with Type 2 diabetes.

People with Type 2 diabetes do not produce or respond normally to insulin, a hormone that regulates the amount of glucose in the blood. Over time, high blood glucose levels can increase the risk for serious complications, including heart disease, blindness, and nerve and kidney damage.

"This approval provides another treatment option for the millions of Americans with Type 2 diabetes," said Mary Parks, M.D., director of the Division of Metabolism and Endocrinology Products in the FDA's Center for Drug Evaluation and Research. "It is effective when used alone or when added to existing treatment regimens."

Type 2 diabetes is the most common form of the disease, affecting between 90 percent and 95 percent of the 24 million people in the United States with diabetes. Tradjenta increases the level of hormones that stimulate the release of insulin after a meal by blocking the enzyme dipeptidyl peptidase 4 or DPP-4, which leads to better blood glucose control.

Tradjenta was demonstrated to be safe and effective in eight double-blind, placebo-controlled clinical studies involving about 3,800 patients with Type 2 diabetes. The studies showed improvement in blood glucose control compared with placebo.

Tradjenta has been studied as a stand-alone therapy and in combination with other Type 2 diabetes therapies including metformin, glimepiride, and pioglitazone. Tradjenta has not been studied in combination with insulin, and should not be used to treat people with Type 1 diabetes or in those who have increased ketones in their blood or urine (diabetic ketoacidosis).

Tradjenta will be dispensed with an FDA-approved Patient Package Insert that explains the drug's uses and risks. The most common side effects of Tradjenta are upper respiratory infection, stuffy or runny nose, sore throat, muscle pain, and headache.

Tradjenta is marketed by Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Conn., and Indianapolis-based Eli Lilly Co.

For more information:

- Type 2 Diabetes[1]
- Approved Drugs: Questions and Answers[2]

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