Drug Utilization Review Board

Oklahoma Health Care Authority
4545 North Lincoln Boulevard, Suite 124
Oklahoma City, Oklahoma 73105
OHCA Board Room

Wednesday
September 10, 2008
6:00 p.m.

THE UNIVERSITY OF OKLAHOMA

MEMORANDUM

TO: Drug Utilization Review Board Members

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

SUBJECT: **Packet Contents for Board Meeting – September 10, 2008**

DATE: September 4, 2008

NOTE: **THE DUR BOARD WILL MEET AT 6:00 P.M.**

Enclosed are the following items related to the September 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 Erythropoiesis Stimulating Agents – **See Appendix C.**

Action Item – Vote to Prior Authorize Protonix® Suspension– **See Appendix D.**

Action Item – Vote to Prior Authorize Patanase® **– See Appendix E.**

Hemophilia Presentation by Guest Speaker: Sarah M. Hawk, P.A.-C. – **See Appendix F.**

60 Day Notice to Prior Authorize Rescue HFA Products – **See Appendix G.**

FDA and DEA Updates – **See Appendix H.**

Future Business

Adjournment

Drug Utilization Review Board

(DUR Board)

Meeting – September 10, 2008 @ 6:00 p.m.

Oklahoma Health Care Authority
4545 N. Lincoln Suite 124
Oklahoma City, Oklahoma 73105
Oklahoma Health Care Authority Board Room

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. McNeill, Chairman:

1. Call To Order

A. Roll Call – Dr. Graham

Items to be presented by Dr. McNeill, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers and Agenda Item

Items to be presented by Dr. McNeill, Chairman:

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

A. August 13, 2008 DUR Minutes – Vote
B. August 14, 2008 DUR Recommendations Memorandum

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

4. Update on DUR/MCAU Program – See Appendix B.

A. Retrospective Drug Utilization Review Responses for February 2008
B. Medication Coverage Activity Audit for August 2008
C. Help Desk Activity Audit for August 2008

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

5. Vote to Prior Authorize Erythropoiesis Stimulating Agents – See Appendix C.

A. COP Recommendations

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

6. Vote to Prior Authorize Protonix® Suspension – See Appendix D.

A. Current PA Criteria
B. COP Recommendations

Items to be presented by Dr. Browning, Dr. McNeill, Chairman

7. Vote to Prior Authorize Patanase® – See Appendix E.

A. Product Summary
B. COP Recommendations

Guest Speaker

8. Hemophilia Presentation by Sarah M. Hawk, P.A.-C., Oklahoma Center for Bleeding and Clotting Disorders – See Appendix F.

A. Utilization Review

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

9. 60 Day Notice to Prior Authorize Rescue HFA Products – See Appendix G.

A. Product Summary
B. Utilization Review
C. COP Recommendations

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

10. FDA and DEA Updates – See Appendix H.

11. Future Business

A. Antidepressants
B. Oral Antifungal Utilization Review
C. Glaucoma Intervention Report
D. Annual Reviews
E. New Product Reviews

12. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES of MEETING of August 13, 2008

BOARD MEMBERS:	PRESENT	ABSENT
Brent Bell, D.O., D.Ph.	X	
Jay D. Cunningham, D.O.		X
Mark Feightner, Pharm.D.		X
Dorothy Gourley, D.Ph.	X	
Evelyn Knisely, Pharm.D.	X	
Thomas Kuhls, M.D.	X	
Dan McNeill, Ph.D., PA-C; Chairman		X
Cliff Meece, D.Ph.; Vice-Chairman	X	
John Muchmore, M.D., Ph.D.	X	
James Rhymer, D.Ph	X	

COLLEGE of PHARMACY STAFF:	PRESENT	ABSENT
Leslie Browning, D.Ph.; PA Coordinator	X	
Metha Chonlahan, D.Ph.; Clinical Pharmacist	X	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	X	
Shellie Keast, Pharm.D.; DUR Manager	X	
Ronald Graham, D.Ph.; Pharmacy Director	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
Visiting Pharmacy Students: Christy Tran, Valerie Pham	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
Lynn Mitchell, M.D., M.P.H,; Director of Medicaid/Medical Services		X
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	X	
Howard Pallotta, J.D.; Director of Legal Services		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:

Rebecca King, Taro	Randy Clifton, Amgen	Jacque Collier, Abbott
James Lieurence, Abbott	Wayne McGuire, NAMI	David Barton, Schering Plough
Bobby White, UCB	Richard Ponder, J&J	Sue Watson, OBI
Justin Caudle, OBI	Joseph Medina, Sepracor	Carl Rose, Sepracor
Jim Fowler, Astra Zeneca	Krici Mohr, Amgen	Vince Morrison, Forest
Linda Cantu, BMS	Susan Stone, Allergan	William Dozier, Gilead
Bruce Robertson, Eli Lilly	Lean Stewart, Merck	

PRESENT FOR PUBLIC COMMENT:

Agenda Item No. 6: Howard Ozer, M.D.; U. of Oklahoma and Sue Watson, Pharm.D.; Ortho Biotech

AGENDA ITEM NO. 1: **CALL TO ORDER**

1A: Roll Call

Dr. Meece called the meeting to order. Roll call by Dr. Graham established a quorum.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 2: **PUBLIC COMMENT FORUM**

Dr. Meece recognized the speakers for public comment.

Agenda Item No. 6: Howard Ozer, M.D.; U. of Oklahoma and Sue Watson, Pharm.D.; Ortho Biotech

For Public Comment, Howard Ozer, M.D.: Thanks very much for the opportunity to speak to you. My name's Howard Ozer. I'm the Eason Chair and Chief of Hematology and Oncology at the University of Oklahoma and wanted to make a few comments about the erythropoeitic growth factors. I have chaired the national ASCO Committee on white cell growth factors for a number of years and still remain as co-chair. I've also done quite a bit of work in publications and clinical trials both with Amgen that produces Aranesp and with J&J/Ortho that produces Procrit. I know a lot about their use in malignant disease but if you like I could also address their use in chronic kidney disease and HIV. We use these factors to a significant degree in our clinic setting and we find them very useful. They must be used by label and there's been a lot of controversy about their use which primarily results from non-label utilization. When the label is followed, they're extremely valuable to our patients. Typical examples will be patients particularly on, they must be patients on chemotherapy and particularly if they're on platinum-containing chemotherapy which we would use, for example, in lung cancer, GYN malignancies, etc. Those patients develop a very severe anemia that results from lack of native erythropoietin production, and so these products are useful in increasing the serum erythropoietin level and decreasing the transfusion requirement. And that's their primary benefit. There's been lots of efforts made to demonstrate they also improve quality of life and there are some data that support that strongly, but their primary value is in decreasing the need for blood transfusions and those costs. Not everyone benefits. If a patient for example, only needs a transfusion every twelve months or so, there's not much use in keeping them chronically on it but if a patient does require multiple transfusions, they are extremely valuable. The two products that are currently on the market are Procrit, which is administered weekly, and Aranesp, which is a long-acting form and is administered every three weeks. The cost is almost equivalent and there are a couple of studies, and I brought one from 2008 if you'd like to see, that demonstrates that the cost is virtually identical for the two products. We do not find that one product is preferable over the other. They each work. It's simply a matter of patient and physician preference in terms of administration. They are also valuable in other settings where anemia may be severe. So we do use them, obviously, in HIV, obviously in chronic renal disease, where the organ, the juxtaglomerular apparatus is not functioning and erythropoietin is not being produced. But there also are a number of sort of, they're not off-label, but they're what we call compendia listings where we might want to use it in myelodysplastic syndromes. Those are similar to leukemia. It's a failure to produce specifically in this case, red blood cells and those patients may also respond and we find it valuable in that setting. With that, I'll be happy to address any questions that you have. I hope I've been brief and relatively clear.

Board Member Kuhls: Just a quick question. What's your feeling about the importance of if you have a curative cancer that you shouldn't use these products?

Dr. Ozer: I'll give you ..... it's a relatively long answer and I'll try and be as brief as I can. There are data that have been generated from Phase 3 studies, relatively small studies, in which patients with breast cancer, potentially curable, and with head and neck cancer, and then a couple of other trials where there has been a decrease in overall survival in the arm that received the erythropoietin product. And actually there have been three products used in those studies. One was a drug that has never become commercial in this country. We don't know how to explain that. As I look at the data, I'm very skeptical of it. That said, I think that if I had a candidate for chemotherapy that I expected to cure, let's say a small tumor in the breast, who's going to get adjunctive chemotherapy, I would probably prefer to transfuse that patient as opposed to giving an erythropoietin product. So I would make that personal choice. The way the FDA has worded the new black box warning, they still allow appropriate use and you could make the argument that a patient with breast cancer might be curable or might live a long time under other circumstances, but if they had profound anemia, and you expected a relatively short survival, it would still be okay as a physician to try that. But I think if I have a young person and I'm on service this month ..... we have a 29-year old who has a Ewing's sarcoma and that patient is required multiple transfusions and we have elected not to treat that patient with an erythropoietic product for exactly that reason. I think the data are still unclear and I think it'll be three or four more years before some of the trials that are testing this really reveal what's going on.

Board Member Kuhls: We spend so much time dealing with cost versus benefit, and really using these agents, to me, is not a cost issue at all, but probably even more importantly the question, because the question of safety has come up, we're really dealing with this more from the safety aspect than anything else. And so my question to you is very simply, is obviously we want to decrease the amount of off-label use and try to use this medication as safely possible in the State of Oklahoma, like I'm sure you do. None of your patients you decide that morning that you need a ..... this product or whatever, erythropoietin, or whatever. There's always time to get a PA and to make sure that there's somebody at a State level looking that it's being used appropriately, right?

Dr. Ozer: I think that's a fair statement. I don't think that there's emergency use of this compound. I don't think that it's going to deflect a transfusion that is required in three or four days. What it can do is prevent transfusions over a period of several months, so I think there's enough time to have an evaluation.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 3: **APPROVAL OF DUR BOARD MINUTES**

3A: July 9, 2008 DUR Minutes

Dr. Gourley moved to approve minutes as submitted; seconded by Dr. Bell.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 4: **UPDATE ON DUR/MCAU PROGRAM**

4A: Retrospective Drug Utilization Review Report: April 2008

4B: Retrospective Drug Utilization Review Responses: January 2008

4C: Medication Coverage Activity Audit: July 2008

4D: Help Desk Activity Audit: July 2008

Reports included in agenda packet; presented by Dr. Keast. Board requested to see Lock-In Program reports at future meetings.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE VOLTAREN® GEL**

Materials included in agenda packet; presented by Dr. Patel.

Dr. Kuhls moved to approve; seconded by Dr. Rhymer.

ACTION: MOTION CARRIED.

AGENDA ITEM NO. 6: **30-DAY NOTICE TO PRIOR AUTHORIZE ERYTHROPOIESIS STIMULATING AGENTS**

For Public Comment, Sue Watson, Pharm.D.: My name is Sue Watson. I'm with, I'm a Pharm.D. with Ortho Biotech, Director of Outcomes Research. We recently had a package update on August 7th so I'm here to answer any questions if you have any label change questions and also just to note in Option 2 that you have, that you'll be discussing, the CKD patients of Dr. Ozer had mentioned, these patients are on these products for the rest of their lives, typically, and they will be getting this product continually until they no longer, when they die. So an 8-week approval of every eight weeks might be quite onerous for CKD patient. I just wanted to mention that. Do you have any questions?

Board Member Kuhls: Other than that, how do you feel about Option 2?

Dr. Watson: I think Option 2 is very in line, it's accurate, it's with the label. You know, my only concern would be number 2 on the eight weeks for CKD patients or ESRD patients. So I guess that would lead you to Option 3, right? Because they would be exempt in Option 3.

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

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 7: **30-DAY NOTICE TO PRIOR AUTHORIZE PATANASE®**

Materials included in agenda packet; presented by Dr. Browning.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 8: **ANNUAL REVIEW OF ANTIULCER PBPA CATEGORY AND 30-DAY NOTICE TO PRIOR AUTHORIZE PROTONIX® SUSPENSION**

Materials included in agenda packet; presented by Dr. Moore.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 9: **QUALAQUIN® ANNUAL REVIEW**

Materials included in agenda packet; presented by Dr. Patel.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 10: **WHITE PAPER ON BIOEQUIVALENT MEDICATIONS**

Materials included in agenda packet; presented by Dr. Le.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 11: **FDA & DEA UPDATES**

Materials included in agenda packet; presented by Dr. Graham.

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 12: **FUTURE BUSINESS**

Materials included in agenda packet; submitted by Dr. Graham.

12A: Antidepressants
12B: Oral Antifungals Utilization Review
12C: Hemophilia Review
12D: Annual Reviews
12E: Glaucoma Intervention Report
12F: New Product Reviews

ACTION: NONE REQUIRED.

AGENDA ITEM NO. 13: **ADJOURNMENT**

The meeting was adjourned at 7:35 p.m.

The University of Oklahoma College of Pharmacy

Pharmacy Management Consultants
ORI W-4403; PO Box 26901
Oklahoma City, OK 73190
(405)-271-9039

Memorandum

Date: August 14, 2008

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

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

Subject: DUR Board Recommendations from Meeting of August 13, 2008

Recommendation 1: Vote to Prior Authorize Voltaren® Gel

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends prior authorization of Voltaren® Gel and placement in the Tier 2 NSAID product. Approval will be based on clinical documentation of inability to take Tier 1 products and supporting information regarding the medical necessity of a topical formulation.

Recommendation 2: Annual Review of Antiulcer PBPA Category

NO ACTION REQUIRED

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

Recommendation 3: Annual Review of Qualaquin®

NO ACTION REQUIRED

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

Appendix B

Retrospective Drug Utilization Review Report

Claims Reviewed for February 2008

Module	Drug Interaction	Duplication of Therapy	Drug-Disease Precautions	Dosing & Duration
Limits which were applied	Established, Major, Males and Females, Age 0-18	Narcotics, Males and Females, Age 26-28	Contraindicated, Asthma, Males and Females, Age 47-49	High Dose, Abilify and Geodon, Males and Females, Age 7-12

Response Summary (Prescriber)
Letters Sent: 86
Response Forms Returned: 43

The response forms returned yielded the following results:

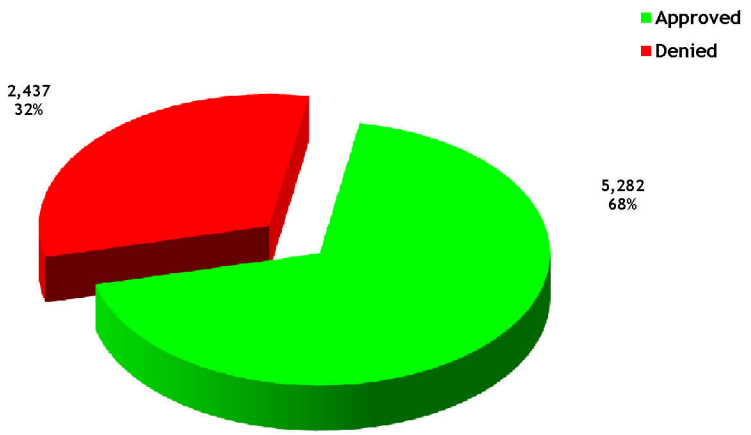
3 (7%)	*Record Error—Not my patient.*
9 (21%)	*No longer my patient.*
2 (5%)	*Medication has been changed prior to date of review letter.*
13 (30%)	*I was unaware of this situation & will consider making appropriate changes in therapy.*
6 (14%)	*I am aware of this situation and will plan to continue monitoring therapy.*
10 (23%)	*Other*

Response Summary (Pharmacy)
Letters Sent: 1
Response Forms Returned: 0

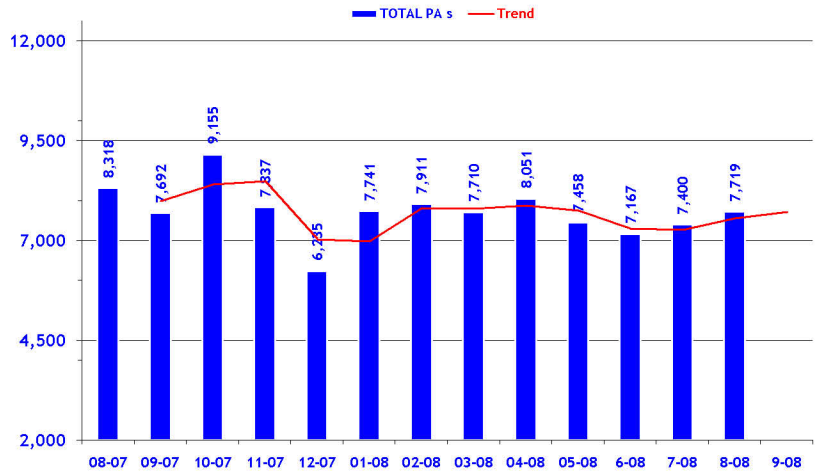
The response forms returned yielded the following results:

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

PRIOR AUTHORIZATION ACTIVITY REPORT
August 2008



PRIOR AUTHORIZATION REPORT
August 2007 – August 2008



Activity Audit for

August 01, 2008 Through August 31, 2008

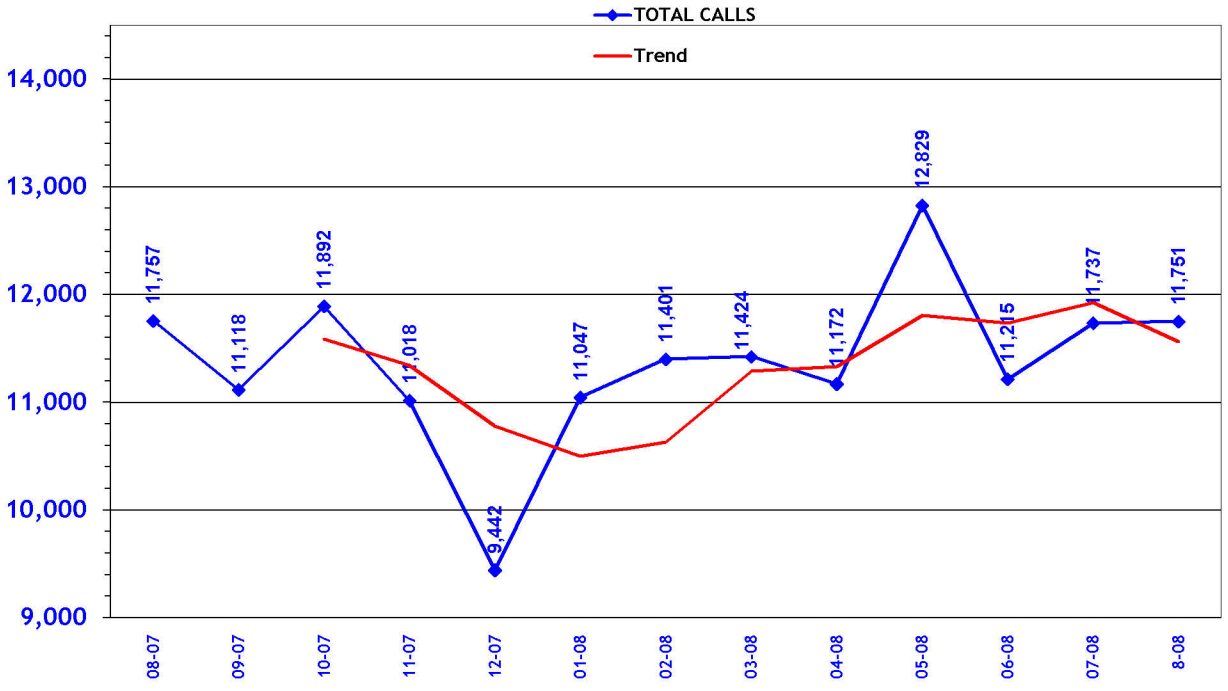
	Average Length of Approvals in Days	Approved	Denied	Total
ACE Inhibitors	24	11	2	13
Angiotensin Receptor Antagonist	339	29	81	110
Antidepressant	270	190	236	426
Antihistamine	94	213	190	403
Antiulcers	41	12	8	20
Anxiolytic	95	2,885	458	3,343
Calcium Channel Blockers	15	12	4	16
Growth Hormones	176	45	1	46
HTN Combos	235	7	9	16
Hypnotics	0	0	1	1
Insomnia	103	68	92	160
Nsaids	316	28	55	83
Plavix	358	88	22	110
Stimulant	209	598	243	841
Others	90	1,095	1,035	2,130
Emergency PAs		1	0	1
Total		**5,282**	**2,437**	**7,719**
Overrides				
Brand	278	20	18	38
Dosage Change	9	371	22	393
High Dose	150	5	0	5
Lost/Broken Rx	13	83	12	95
Nursing Home Issue	7	42	3	45
Other	10	40	2	42
Quantity vs. Days Supply	150	14	5	19
Stolen	3	11	0	11
Wrong D.S. on Previous Rx	0	0	1	1
Overrides Total		**586**	**63**	**649**

Denial Reasons

Lack required information to process request.	1,824
Unable to verify required trials.	1,127
Does not meet established criteria.	173
Not an FDA approved indication/diagnosis.	137
Considered duplicate therapy. Member has a prior authorization for similar medication.	128
Member has active PA for requested medication.	68
Requested dose exceeds maximum recommended FDA dose.	60
Medication not covered as pharmacy benefit.	15
Drug Not Deemed Medically Necessary	7
Duplicate Requests	641
* Changes to existing	776

** Changes to existing PA's: Backdates, changing units, end dates, etc.*

CALL VOLUME MONTHLY REPORT
August 2007 – August 2008



Appendix C

Vote to Prior Authorize ESAs

Oklahoma Health Care Authority

September 2008

Recommendations

The College of Pharmacy recommends prior authorization of ESAs with the following criteria:

1. FDA approved indication for specific products.
    a. Treatment of Anemia of Chronic Renal Failure Patients
    b. Treatment of Anemia in Zidovudine-treated HIV-infected Patients
    c. Treatment of Anemia in Cancer Patients on Chemotherapy
        i. Myelosuppressive Chemotherapy-Induced Anemia (Hb 8-10 g/dL) Non-Curative
    d. Reduction of Allogeneic Blood Transfusion in Surgery Patients
2. Most recent Hb levels (and date obtained) should be included on petition. Each approval will be for 8 weeks in duration. Authorization can be granted for up to 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen. Authorization for surgery patients will be for a maximum of 4 weeks.
3. Continuation Criteria:
    a. Continue dose if Hb is ≤ 12.0 g/dL.
    b. If Hb is increasing and approaching 12 g/dL then reduce dose by at least 25%.
    c. If more than 1 g/dL increase (but Hb not greater than upper limits listed below) has occurred in a 2 week period reduce dose by 25 to 50 %.
4. Discontinuation Criteria:
    a. ESRD – Discontinue treatment if Hb is at or above 13.0 g/dL.
    b. All others – Discontinue treatment if Hb is at or above 12 g/dL.
    c. If a minimum increase of 1 g/dL has not been achieved after initial 8 weeks of therapy.
5. Reinitiation Criteria:
    a. If Hb decreases to ≤ 10 g/dL then therapy may be reinitiated at 25 to 50% of the prior dose.

New prior authorization forms for the initial and continuation requests for these medications will be implemented. A copy of these forms will be available at the DUR Board meeting for review. Once the initial request has been submitted and approved, continuation of therapy may occur with submission of the continuation form.

Appendix D

Vote to Prior Authorize Protonix Suspension®

Oklahoma Health Care Authority
September 2008

Anti-Ulcer Medications	
The following products requires prior authorization with a special reason for use: ▪ **ranitidine (Zantac®) – effervescent tablets and capsules** ▪ **brand omeprazole 40mg (Prilosec® 40mg caps)**	
Tier 1	Tier 2
omeprazole (10 and 20 mg caps)	**esomeprazole (Nexium® Caps and I.V.)***
omeprazole/antacid (Zegerid® Caps)	**omeprazole/antacid (Zegerid® Packets)***
lansoprazole (Prevacid®) capsules	**lansoprazole (Prevacid® ODT and Granules)***
	pantoprazole sodium (Protonix® Tabs, Oral Suspension, and I.V.)*

Color indicates Supplemental Rebate Participation
***Special dosage forms require reason for use.**

Approval Criteria

- Documented recent trial of a Tier-1 medication with inadequate results or adverse effect, or
- Documented contraindication to the Tier-1 medications, or
- Documented FDA-approved indication for which Tier-1 products are not indicated

Recommendations

The College of Pharmacy recommends placing Protonix® Oral Suspension in Tier 2 of the Anti-ulcers PBPA Category. Approval requires documentation of medical necessity for this dosage form over available Tier 1 products. Quantity limit of 30 packets for 30 days would also be applied.

Appendix E

Vote to Prior Authorize Patanase® (olopatadine hydrochloride)

Oklahoma Health Care Authority
September 2008

Manufacturer	Alcon Laboratories, Inc.
Classification	H_1 receptor antagonist nasal spray
Status:	Prescription Only

Summary

Patanase® (olopatadine) is an antihistamine with selective H1 receptor antagonist activity available as a 0.6% nasay spray (665mcg of olopatadine hydrochloride in each 100-microliter spray). It is specifically indicated for symptomatic relief of seasonal allergic rhinitis in patients 12 years of age and older. Patanase® is available in a 30.5g bottle that contains 240 actuations. The recommended dose is two sprays per nostril twice a day.

Recommendations

The College of Pharmacy recommends prior authorization of Pantanase® and placement as a Tier 3 nasal allergy product. Approval will be based on the following criteria:

1. The following criteria are required for approval of a Tier 2 product (or a Tier 3 product if no Tier 2 exists):
    a. Documented adverse effect or contraindication to the preferred products.
    b. Failure with at least two Tier 1 medications defined as no beneficial response after at least two weeks each of use during which time the drug has been titrated to the recommended dose (all available Tier 1 corticosteroids should be tried prior to approval of higher Tiered products).
2. The following criteria are required for approval of a Tier 3 product:
    a. All Tier 2 criteria must be met.
    b. Failure with all available Tier 2 products defined as no beneficial response after at least two weeks each of use during which time the drug has been titrated to the recommended dose.
3. Approvals will be for the duration of three months, except for members with chronic diseases such as asthma or COPD, in which case authorizations will be for the duration of one year.

Appendix F

Anti-Hemophilia Agents

Oklahoma HealthCare Authority
September 2008

Fiscal Year Comparison

Fiscal Year	Members	Claims	Cost	Cost/Claim	Units	Days
2007	70	732	$19,353,278.78	$26,438.91	13,397,466	10,255
2008	65	618	$22,927,871.02	$37,100.11	14,956,209	9,447
Change	-5	-114	$3,574,592.24	$10,661.20	1,558,743	-808
Percent Change	-7.1%	-15.6%	18.5%	40.3%	11.6%	-7.9%

Summary of Utilization for Fiscal Year 2008

Type	Medication	Claims	Cost	Cost/Unit	Cost/Claim	% Cost
AICC	FEIBA VH	79	$6,690,147.33	$1.88	$84,685.41	29.2%
r Factor VIIa	NOVOSEVEN	45	$7,865,507.07	$1.48	$174,789.05	34.3%
r Factor VIII	KOGENATE FS	249	$3,294,992.86	$1.52	$13,232.90	14.4%
r Factor VIII	ADVATE	86	$2,671,717.59	$1.54	$31,066.48	11.7%
r Factor VIII	RECOMBINATE	31	$314,924.26	$1.14	$10,158.85	1.4%
h Factor VIII/vWF	ALPHANATE	39	$1,395,745.65	$1.16	$35,788.35	6.1%
h Factor VIII/vWF	HUMATE-P	13	$48,877.08	$1.08	$3,759.78	0.2%
h Factor VIII:c	MONOCLATE-P	4	$35,490.20	$0.92	$8,872.55	0.2%
r Factor IX	BENEFIX	70	$590,840.34	$0.96	$8,440.58	2.6%
h Factor IX	MONONINE	2	$19,628.64	$0.79	$9,814.32	0.1%
TOTALS		618	$22,927,871.02	$1.53	$37,100.11	100%

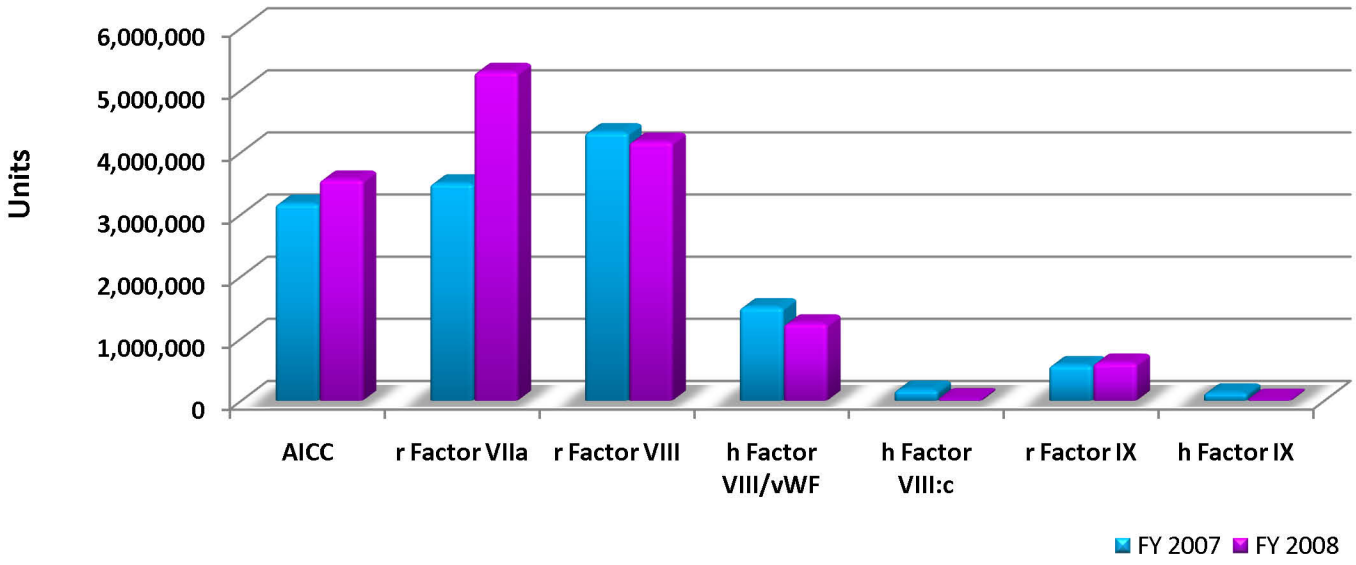
AICC = Anti-Inhibitor Coagulation Complex, **r** =recombinant, **h** =human, **vWF** =von Willibrand Factor, **c** =coagulant

Summary of Utilization for Fiscal Year 2007

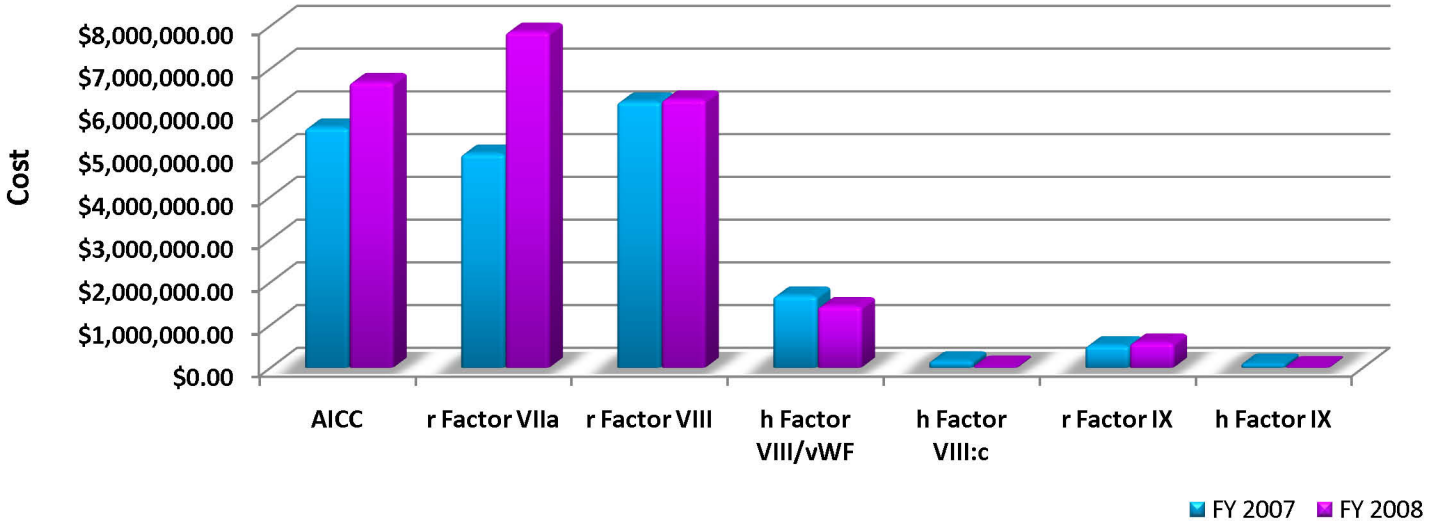
Type	Medication	Claims	Cost	Cost/Unit	Cost/Claim	% Cost
AICC	FEIBA VH	73	$5,621,551.94	$1.77	$77,007.56	29.0%
r Factor VIIa	NOVOSEVEN	45	$5,012,659.71	$1.43	$111,392.44	25.9%
r Factor VIII	KOGENATE-FS	358	$4,053,861.33	$1.47	$11,323.64	20.9%
r Factor VIII	ADVATE	71	$1,815,959.74	$1.54	$25,576.90	9.4%
r Factor VIII	RECOMBINATE	43	$360,504.01	$0.95	$8,383.81	1.9%
h Factor VIII/vWF	ALPHANATE	38	$1,630,626.98	$1.12	$42,911.24	8.4%
h Factor VIII/vWF	HUMATE-P	15	$60,541.55	$1.10	$4,036.10	0.3%
h Factor VIII:c	MONOCLATE-P	9	$165,907.21	$0.92	$18,434.13	0.9%
r Factor IX	BENEFIX	68	$526,752.15	$0.92	$7,746.36	2.7%
h Factor IX	MONONINE	12	$104,914.16	$0.79	$8,742.85	0.5%
TOTALS		732	$19,353,278.78	$1.44	$26,438.91	45.1%

AICC = Anti-Inhibitor Coagulation Complex, **r** =recombinant, **h** =human, **vWF** =von Willibrand Factor, **c** =coagulant

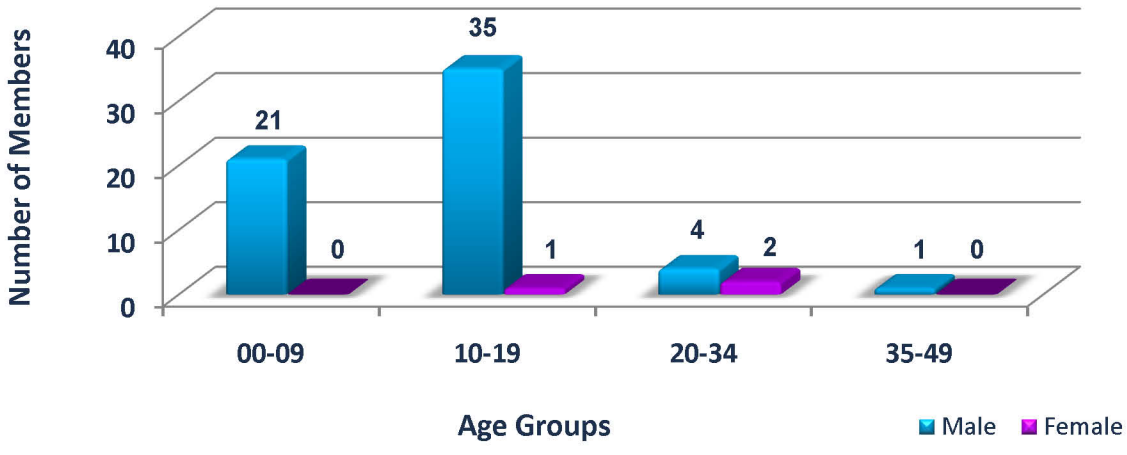
Comparison of Units Utilized between FY 2008 and FY 2007



Comparison of Costs between FY 2008 and FY 2007



Demographics of Members Utilizing Anti-Hemophilic Agents: FY 2008



Utilization Details – Fiscal Year 2008

Medication	Claims	Units	Days	Members	Cost	Units/Day	Claims/Mem	% Cost	Cost/Claim
FEIBA VH INJ IMMUNO	79	3,562,678	1,761	5	$6,690,147.33	2,023	15.8	29.18%	$84,685.41
NOVOSEVEN INJ 4800MCG	26	4,430,400	689	3	$6,581,057.66	6,430	8.67	28.70%	$253,117.60
NOVOSEVEN INJ 1200MCG	16	777,600	416	3	$1,154,992.48	1,869	5.33	5.04%	$72,187.03
NOVOSEVEN INJ 2400MCG	3	88,800	35	3	$129,456.93	2,537	1	0.56%	$43,152.31
KOGENATE FS INJ 1000UNIT	33	640,204	393	11	$986,039.11	1,629	3	4.30%	$29,879.97
KOGENATE FS INJ 1000/BS	42	614,936	614	5	$947,175.74	1,002	8.4	4.13%	$22,551.80
KOGENATE FS INJ 500/BS	50	385,231	718	6	$593,463.24	537	8.33	2.59%	$11,869.26
KOGENATE FS INJ 500UNIT	39	223,703	414	18	$320,567.17	540	2.17	1.40%	$8,219.67
KOGENATE FS INJ 250UNIT	42	104,876	440	16	$161,673.34	238	2.63	0.71%	$3,849.37
KOGENATE FS INJ 2000/BS	2	52,450	40	2	$80,779.30	1,311	1	0.35%	$40,389.65
KOGENATE FS INJ 250/BS	41	141,309	562	8	$205,294.96	251	5.13	0.90%	$5,007.19
ADVATE INJ 2000UNIT	16	752,713	288	2	$1,159,236.12	2,614	8	5.06%	$72,452.26
ADVATE INJ 1500UNIT	17	402,322	444	2	$619,646.43	906	8.5	2.70%	$36,449.79
ADVATE INJ 1000UNIT	12	224,358	207	4	$345,561.12	1,084	3	1.51%	$28,796.76
ADVATE INJ 3000UNIT	5	147,870	58	1	$227,740.55	2,549	5	0.99%	$45,548.11
ADVATE INJ 500UNIT	21	147,148	381	4	$226,291.88	386	5.25	0.99%	$10,775.80
ADVATE INJ 250UNIT	13	48,934	187	3	$75,412.31	262	4.33	0.33%	$5,800.95
ADVATE INJ 500UNIT	2	11,572	30	1	$17,829.18	386	2	0.08%	$8,914.59
RECOMBINATE INJ 801-1240	11	159,406	89	3	$194,517.53	1,791	3.67	0.85%	$17,683.41
RECOMBINATE INJ 401-800	14	94,529	177	3	$98,682.47	534	4.67	0.43%	$7,048.75
RECOMBINATE INJ 220-400	6	22,610	65	3	$21,724.26	348	2	0.09%	$3,620.71
ALPHANATE INJ VWF/HUM	6	409,200	165	1	$496,957.38	2,480	6	2.17%	$82,826.23
ALPHANATE INJ	7	445,070	182	3	$489,606.05	2,445	2.33	2.14%	$69,943.72
ALPHANATE INJ VWF/HUM	2	111,900	60	1	$135,899.66	1,865	2	0.59%	$67,949.83
ALPHANATE INJ 250-500	6	25,600	60	1	$28,184.90	427	6	0.12%	$4,697.48
ALPHANATE INJ VWF/HUM	9	63,840	210	2	$55,053.16	304	4.5	0.24%	$6,117.02
ALPHANINE SD INJ 250-1500	9	145,890	44	1	$190,044.50	3,316	9	0.83%	$21,116.06
HUMATE-P INJ 1000UNIT	3	21,352	18	1	$22,370.28	1,186	3	0.10%	$7,456.76
HUMATE-P INJ 500UNIT	2	9,536	12	1	$10,497.90	795	2	0.05%	$5,248.95
HUMATE-P SOL 1200UNIT	4	8,186	23	2	$9,017.20	356	2	0.04%	$2,254.30
HUMATE-P INJ 2000UNIT	2	3,768	12	1	$4,153.10	314	2	0.02%	$2,076.55
MONOCLATE-P INJ 1000UNIT	4	38,400	20	1	$35,490.20	1,920	4	0.15%	$8,872.55
BENEFIX INJ 1000UNIT	36	340,622	295	8	$320,272.48	1,155	4.5	1.40%	$8,896.46
BENEFIX INJ 2000UNIT	10	180,740	118	1	$179,769.36	1,532	10	0.78%	$17,976.94
BENEFIX INJ 500UNIT	18	81,844	171	3	$79,474.33	479	6	0.35%	$4,415.24
BENEFIX INJ 250UNIT	6	11,772	35	4	$11,324.17	336	1.5	0.05%	$1,887.36
MONONINE INJ 1000UNIT	2	24,840	9	1	$19,628.64	2,760	2	0.09%	$9,814.32
TOTALS	**618**	**14,956,209**	**9,447**	**65***	**$22,927,871.02**	**1,583**	**9.51**	**100%**	**$37,100.11**

*Total number of unduplicated members

Utilization Details – Fiscal Year 2007

Medication	Claims	Units	Days	Members	Cost	Units/Day	Claims/Mem	% Cost	Cost/Claim
FEIBA VH INJ IMMUNO	73	3,175,119	1,340	5	$5,621,551.94	1,920	14.6	29.05%	$77,007.56
NOVOSEVEN INJ 4800MCG	15	2,179,200	424	1	$3,107,490.09	5,140	15	16.06%	$207,166.01
NOVOSEVEN INJ 2400MCG	13	674,400	308	2	$970,539.07	2,190	6.5	5.01%	$74,656.85
NOVOSEVEN INJ 1200MCG	17	648,000	510	2	$934,630.55	1,271	8.5	4.83%	$54,978.27
KOGENATE FS INJ 1000UNIT	78	1,144,474	936	19	$1,604,514.09	1,223	4.11	8.29%	$20,570.69
KOGENATE FS INJ 500UNIT	107	768,841	1,369	24	$1,172,541.23	562	4.46	6.06%	$10,958.33
KOGENATE FS INJ 250UNIT	97	315,200	1,268	22	$448,922.25	249	4.41	2.32%	$4,628.06
KOGENATE FS INJ 500/BS	35	261,895	424	10	$403,463.55	618	3.5	2.08%	$11,527.53
KOGENATE FS INJ 1000/BS	12	178,558	164	3	$275,029.12	1,089	4	1.42%	$22,919.09
KOGENATE FS INJ 250/BS	29	97,681	425	8	$149,391.09	230	3.63	0.77%	$5,151.42
ADVATE INJ 2000UNIT	14	642,620	232	1	$989,688.75	2,770	14	5.11%	$70,692.05
ADVATE INJ 1000UNIT	15	242,901	248	2	$374,129.79	979	7.5	1.93%	$24,941.99
ADVATE INJ 250UNIT	22	25,859	205	5	$39,914.16	126	4.4	0.21%	$1,814.28
ADVATE INJ 500UNIT	1	1,020	2	1	$1,574.95	510	1	0.01%	$1,574.95
ADVATE INJ 500UNIT	15	128,756	213	4	$198,346.49	604	3.75	1.02%	$13,223.10
ADVATE INJ 1500UNIT	4	137,850	60	3	$212,305.60	2,298	1.33	1.10%	$53,076.40
RECOMBINATE INJ 801-1240	17	257,099	190	4	$246,871.01	1,353	4.25	1.28%	$14,521.82
RECOMBINATE INJ 401-800	18	98,587	185	6	$94,715.27	533	3	0.49%	$5,261.96
RECOMBINATE INJ 220-400	8	23,563	87	4	$18,917.73	271	2	0.10%	$2,364.72
ALPHANATE INJ	21	1,245,620	558	4	$1,370,269.15	2,232	5.25	7.08%	$65,250.91
ALPHANATE INJ 250-500	11	50,500	107	1	$55,595.65	472	11	0.29%	$5,054.15
ALPHANINE SD INJ 250-1500	6	157,200	51	1	$204,762.18	3,082	6	1.06%	$34,127.03
HUMATE-P INJ 1000UNIT	1	30,000	10	1	$33,004.15	3,000	1	0.17%	$33,004.15
HUMATE-P SOL 600UNIT	11	19,779	25	5	$21,800.55	791	2.2	0.11%	$1,981.87
HUMATE-P SOL 1200UNIT	3	5,204	7	3	$5,736.85	743	1	0.03%	$1,912.28
MONOCLATE-P INJ 1500UNIT	8	170,765	120	1	$157,820.06	1,423	8	0.82%	$19,727.51
MONOCLATE-P INJ 1000UNIT	1	8,750	5	1	$8,087.15	1,750	1	0.04%	$8,087.15
BENEFIX INJ 1000UNIT	34	448,400	350	4	$410,508.78	1,281	8.5	2.12%	$12,073.79
BENEFIX INJ 500UNIT	16	80,940	160	2	$74,142.69	506	8	0.38%	$4,633.92
BENEFIX INJ 250UNIT	18	45,920	180	2	$42,100.68	255	9	0.22%	$2,338.93
MONONINE INJ 1000UNIT	7	114,045	52	1	$90,114.03	2,193	7	0.47%	$12,873.43
MONONINE INJ 500UNIT	5	18,720	40	1	$14,800.13	468	5	0.08%	$2,960.03
TOTALS	**732**	**13,397,466**	**10,255**	**70***	**$19,353,278.78**	**1,306**	**10.46**	**100%**	**$26,438.91**

*Total number of unduplicated members

Appendix G

60 Day Notice to Prior Authorize Rescue HFA Inhalers

Oklahoma Health Care Authority
September 2008

Introduction

Albuterol inhalers deliver medication directly into the lungs and are used as rescue therapy to treat bronchospasm in patients with asthma and various other diseases of the airways who are able to use inhalers. For decades albuterol has been available on the market in both trade name and generic. However, on December 31, 2008, and pursuant to the Clean Air Act and an international environmental treaty, the Montreal Protocol on Substances that Deplete the Ozone Layer, a four-year long FDA medication withdrawal process will become finalized and the chlorofluorocarbon (CFC) propelled albuterol metered dose inhalers will no longer be produced, marketed, or sold in the United States.

The CFC metered dose inhalers are being replaced by hydrofluoroalkane propelled inhalers, which the FDA has found to be a safe and effective alternative that is also environmentally friendly. The taste, delivery feel, and other attributes of the HFA may differ to that of the CFC propelled products. There are currently three HFA albuterol products and one levalbuterol product available on the market. The following chart compares the HFA rescue products currently available:

Currently Available Products[i]

Product	Contains Alcohol	Contains Oleic Acid	Active drug delivered	Sprays to Prime	Days before Re-Prime	Cleaning Frequency	Age Indicated
Proventil® HFA	Yes	Yes	90mcg	4 Sprays	14 Days	Weekly	4 Years
Ventolin® HFA*	No	No	90mcg	4 Sprays	14 Days	Weekly	4 Years
ProAir® HFA	Yes	No	90mcg	3 Sprays	14 Days	Weekly	12 Years
Xopenex® HFA	Yes	Yes	45mcg	4 Sprays	3 Days	Weekly	4 Years

*Once this product is removed from the foil wrapper it should be discarded in 6 months even if there are sprays remaining in the canister.

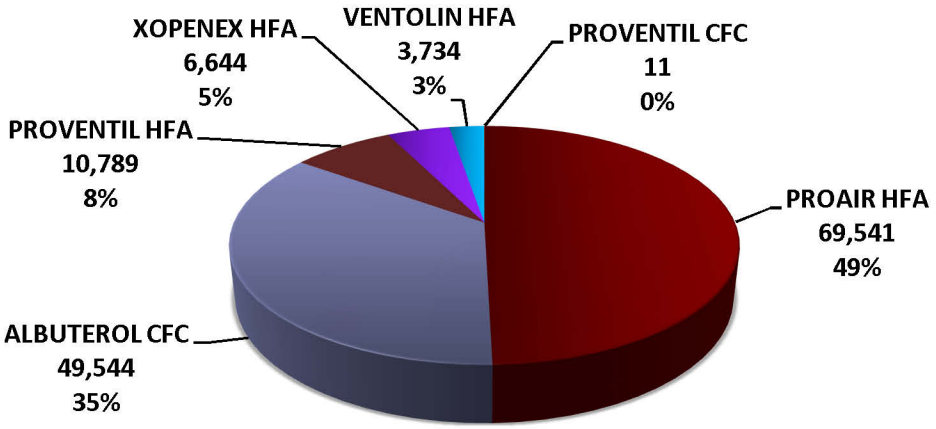
Cleaning recommendations for all products are similar and consists of removing the canister and washing the mouthpiece in running warm water. Excess water should be shaken and mouthpiece should be allowed to air-dry overnight. In case the inhaler is blocked and needs to be washed immediately, wash as above and shake off excess water, then spray two puffs away from the face before use.

Utilization

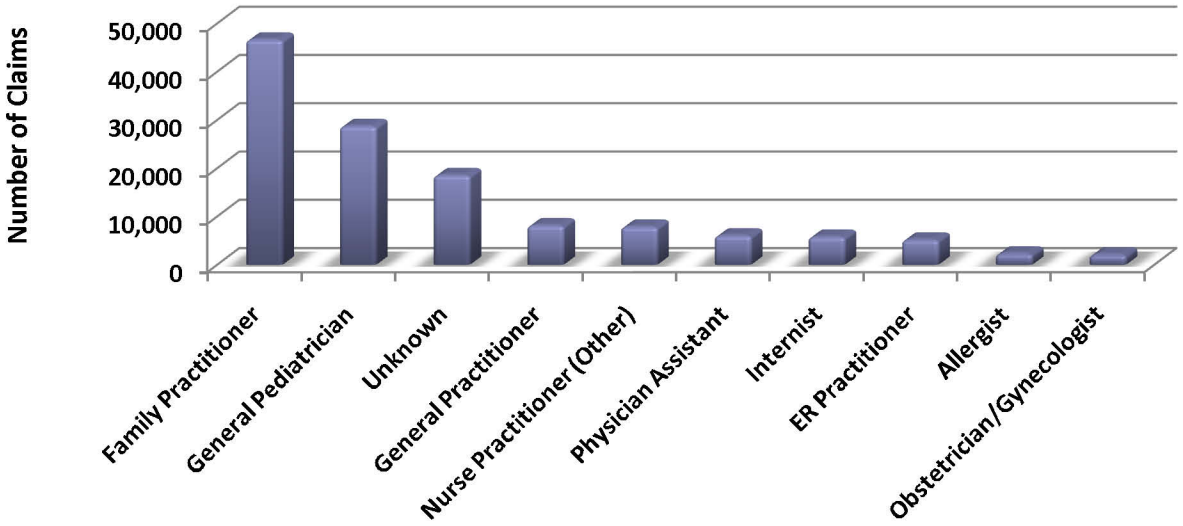
Utilization of Rescue Inhalers during FY 2008

Medication	Claims	Units	Days	Members	Cost	Cost/Claim	Perdiem
PROAIR® HFA	69,541	703,495	1,621,912	32,244	$2,882,043.61	$41.44	$1.78
ALBUTEROL CFC	49,544	996,924	1,151,852	22,859	$1,144,904.85	$23.11	$0.99
PROVENTIL® HFA	10,789	79,395	269,718	6,192	$486,887.09	$45.13	$1.81
XOPENEX® HFA	6,644	116,158	169,561	3,530	$374,841.64	$56.42	$2.21
VENTOLIN® HFA	3,734	77,261	88,481	2,388	$153,314.02	$41.06	$1.73
PROVENTIL® CFC	11	323	298	2	$743.64	$67.60	$2.50
Totals	**140,263**	**1,973,556**	**3,301,822**	**58,880**	**$5,042,734.85**	**$35.95**	**$1.53**

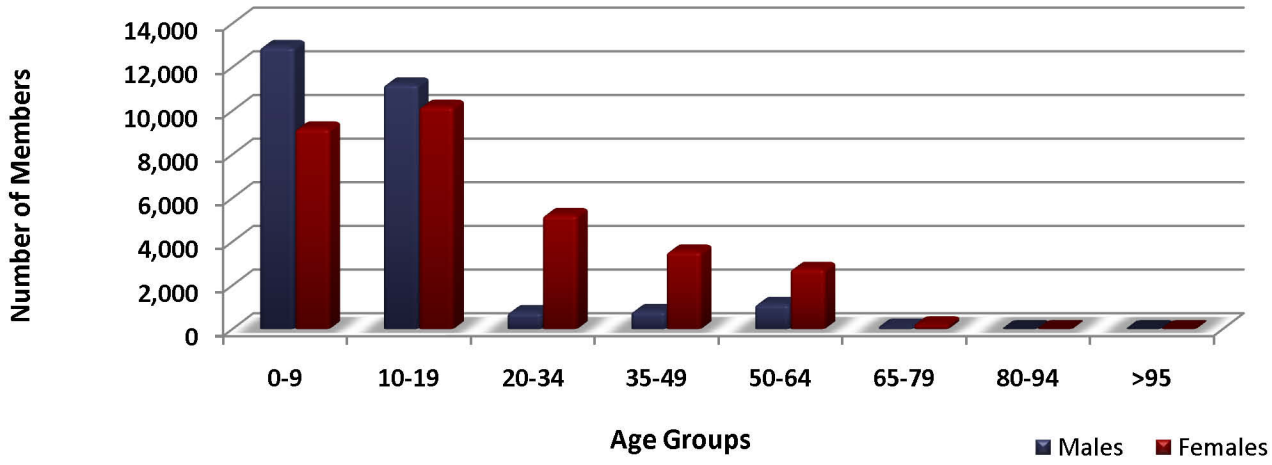
Market Share by Claims during Fiscal Year 2008



Top 10 Prescribers of Rescue Inhalers



Demographics: Fiscal Year 2008



	0-9	10-19	20-34	35-49	50-64	65-79	80-94	>95
Males	12,941	11,229	793	843	1,168	117	2	1
Females	9,208	10,204	5,246	3,571	2,777	252	9	3

516 unknowns

Recommendations

The College of Pharmacy recommends the addition of the Rescue HFA Inhalers to the Product Based Prior Authorization program. This category is unique in that, pharmacologically, all the agents considered consist of a form of albuterol, in an aerosolized delivery device with hydrofluoroalkane as the propellant. Therefore, the College of Pharmacy recommends initiation of a supplemental rebate offer to all manufacturers involved before arrangement of the products in the tier list. The manufacturer(s) returning the best economic offer will subsequently have their product placed on Tier 1, and all others will be placed on Tier 2. If no supplemental rebate offers are returned then the current lowest priced HFA product will be placed on tier-1. Once the Tier 1 product(s) have been determined, the College of Pharmacy will perform an educational outreach activity to inform providers of the FDA mandate and the SoonerCare preferred product(s).

Short Acting B2 Agonists	
Tier 1	**Tier 2**
Best Supplemental Rebate Agreement	**ProAir® HFA**
	Proventil® HFA
	Ventolin® HFA
	Xopenex® HFA

The following is the proposed approval criteria:

1. Approved or clinically accepted indication, and
2. Specific reason member cannot use all available tier one products.

Potential Secondary Costs

Overall efficacy is considered to be equal across this class, but drug selection requires individual patient history which includes, but is not limited to: other illnesses, disease risk factors, and current symptoms. Clinical information for these products will be presented as part of the 30 Day Notice.

Potential Administrative Costs

Based on a potential shift of 100% of all the claims that are currently for the albuterol CFC, it is estimated that up to 11,000 petitions could be required if 50% were to desire a Tier 2 product. With proper planning and notification, the number of petitions could be kept to a minimal depending on which product(s) are Tier 1.

The proposed tier changes would affect approximately 39% of the total population for this PBPA category. However, this population would otherwise be effected as the transition is mandated by the FDA.

Previously, it has been theorized that total cost per petition to the *healthcare system* (includes cost to physicians, pharmacists, and program) is between $7.12 and $13.78. Total cost per petition to the *healthcare system* is estimated to be between $78,320.00 and $151,580.00 annually. Anticipated actual administrative cost to the program is projected to be less than $80,000.

Potential Program Savings

Potential pharmacy reimbursement savings to the program based on recommended tiers and a potential shift of 99% of market share of albuterol CFC to a Tier 1 product is estimated to be $755,838.31. Figure based on current highest and lowest priced products.

Total Potential Savings

Potential Savings:	$755,838.31		$755,838.31
Potential Administrative Cost:	$78,320.00		$151,580.00
Total Potential Reimbursement Savings:	**$677,518.31**	**to**	**$ 604,258.31**

[i] **Clinical Update:Eliminating Chlorofluorocarbons (CFC)-Albuterol**. American College of Allergy, Asthma & Immunology. Available online at: http://www.daadocs.com/warning_docs/CFC-Albuterol.pdf

Appendix H

Information for Healthcare Professionals
Natalizumab Injection for Intraveneous Use (marketed as Tysabri)

FDA ALERT [8/2008]: The FDA has recently received information from the manufacturer about two new cases of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri monotherapy for multiple sclerosis in Europe. Both patients had received Tysabri for more than one year. PML, which is usually fatal, is a known risk of Tysabri treatment, but previous cases in patients with multiple sclerosis were seen in combination with other immunomodulatory therapies. About 39,000 patients have received treatment with Tysabri worldwide, with about 12,000 patients having been treated for at least one year. No new cases have been seen in the US, where about 7,500 patients have received the drug for longer than one year and about 3,300 patients have received the drug for at least one and a half years.

In the U.S., Tysabri is available only to patients with relapsing multiple sclerosis (MS) or Crohn's disease (CD) who are enrolled in the risk minimization plan called the TOUCH Prescribing Program. Under the TOUCH Prescribing Program, every Tysabri-treated patient is closely monitored and followed for the occurrence of PML and other serious opportunistic infections.

While the two patients who developed PML were on monotherapy, the FDA still believes that Tysabri monotherapy may confer a lower risk of PML than when Tysabri is used together with other immunomodulatory medications.

The FDA is working with the manufacturer to amend the product labeling to inform prescribers and patients that cases of PML have occurred in patients taking Tysabri as monotherapy.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program and complete a form online at http://www.fda.gov/medwatch/report.htm or report by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online, (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

Recommendations and Information for Healthcare Professionals registered with the TOUCH Prescribing Program to Consider when Prescribing Tysabri

- The two new cases of PML are notable for being the first cases occurring in the absence of concomitant or recent immunomodulatory therapy (e.g., beta-interferons)
- Although PML and other opportunistic infections are known risks of Tysabri, these are the first cases of PML that have been reported following Tysabri's market re-introduction in June 2006.
- PML is a rare infection of the central nervous system caused by a virus that can affect patients who have a compromised immune system.

- Both of the recently diagnosed patients were receiving Tysabri as monotherapy (one for 14 months and one for 17 months), although one of the patients had a history of prior immunosuppressant therapy with azathioprine and beta-interferons.

- Both patients were diagnosed on the basis of physical findings, MRI findings, and the detection of JC viral DNA in the cerebrospinal fluid.

- The incidence of PML with Tysabri remains unknown, although the available data indicate that the risk of PML when Tysabri is taken as monotherapy is lower than the risk of PML when Tysabri is taken with other immunosuppressant MS treatments.

- Continued clinical vigilance and close monitoring for the signs and symptoms of PML as dictated by the TOUCH Prescribing Program is necessary.

- Tysabri should not be infused if PML is suspected.

Information for Healthcare Professionals and Patients to Consider

- Always talk to your doctor about any medications and over the counter supplements that you may be taking.

- If you and your doctor decide that the benefits of starting Tysabri outweigh possible risks, then you must be enrolled in the TOUCH Prescribing Program before receiving Tysabri. The TOUCH Prescribing Program materials will describe the signs and symptoms of PML you should watch for.

- PML is a rare infection of the brain caused by a polyomavirus, called the JC virus. The JC virus is often acquired during childhood. Most adults have been infected with the JC virus but do not develop PML. The virus appears to remain inactive until something (such as a weakened immune system) allows it to be reactivated and start to multiply. People with a weakened immune system or people taking drugs that suppress their immune system (immunosuppressants) are most likely to get the disease. This virus infects the patient's brain and nervous system when their immune system is not working optimally.

- PML can occur naturally in the course of certain diseases, and it may also occur if someone's immune system has been suppressed by medications. Tysabri is one of the medications that PML has been associated with. Symptoms of PML may be similar to MS, so the diagnosis of PML is made by brain MRI and detection of the virus in the spinal fluid.

- PML symptoms may begin gradually, but they usually worsen rapidly. Symptoms vary depending on which part of the brain is infected. In about two-thirds of patients mental function declines rapidly and progressively, causing dementia. Speaking becomes increasingly difficult. People may become partially blind. Walking may become difficult. Rarely, headaches and seizures occur.

- The two new cases of PML are notable for being the first cases in patients with multiple sclerosis treated with Tysabri who were not also taking beta-interferon therapy.

- Both patients were diagnosed on the basis of physical findings, abnormal MRI findings and the detection of JC viral DNA in the cerebrospinal fluid.

- The risk of developing PML with Tysabri remains unknown, although the available data indicate that the risk of PML when Tysabri is taken as monotherapy is lower than the risk of PML when Tysabri is taken with other treatments that affect your immune system.

- Tysabri should not be given if PML is suspected until further clinical evaluation is performed.

Background and Data Summary

Tysabri, a recombinant humanized monoclonal antibody that binds to α4-integrin, was initially approved by the FDA in November, 2004, but was withdrawn by the manufacturer in February 2005 after three patients in clinical trials (two in MS trials and one in a CD trial) developed PML. The two MS patients were receiving concomitant beta-interferon therapy, and the patient in the CD trial had received immosuppressive therapy prior to receiving Tysabri.

In June 2006, the FDA approved an application for the re-marketing of Tysabri as monotherapy for the treatment of patients with relapsing forms of MS. Tysabri is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies.

In January 2008, Tysabri was approved for inducing and maintaining a clinical response and remission in patients with moderate to severely active CD who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α.

The European cases of PML were reported by Biogen Idec and Elan (the makers and marketers of Tysabri) as follows:

- *Case 1*: This postmarket case of PML occurred in a patient who had received Tysabri monotherapy for 17 months. Prior to treatment, the patient had aggressive MS with high levels of relapse and MRI activity. Signs and symptoms which led to a suspicion of PML included muscle twitching, weakness of the left upper extremity, and brain MRI changes. Tysabri dosing was suspended and the patient underwent cerebrospinal fluid (CSF) testing. The patient has been diagnosed with PML based on the detection of JC viral DNA in the CSF in the setting of these clinical symptoms and MRI findings. Follow up to the case, received by the company on July 31, 2008, reported that this patient is ambulatory and continues to be managed as an outpatient.

- *Case 2*: This postmarket case occurred in a patient who had received Tysabri monotherapy for 14 months. This patient with MS had a long history of treatment with disease-modifying therapies including azathioprine and beta-interferons. Initial clinical features of PML included development of hemiparesis and cognitive symptoms. Brain MRI revealed lesions that were atypical. The diagnosis of PML was confirmed when JC viral DNA was detected in the CSF in the setting of the appropriate clinical signs, symptoms, and MRI features. At the time of reporting, the patient was hospitalized and

in stable condition.

Report serious adverse events to
FDA's MedWatch reporting system by completing a form on line at
http://www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178),
by mail using the postage-paid address form provided online
(5600 Fishers Lane, Rockville, MD 20852-9787),
or by telephone (1-800-FDA-1088).

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Date created: August 25, 2008

Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia)

FDA Investigates a Report from the SEAS Trial

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing this product. FDA is considering but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

FDA is investigating a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of a possible association between the use of Vytorin (a combination of simvastatin plus ezetimibe) and a potentially increased incidence of cancer. Simvastatin (Zocor), a "statin" class drug approved in 1991, decreases production of cholesterol by the liver and is indicated to reduce LDL-cholesterol levels and reduce the risk of cardiovascular events such as heart attack and stroke. Ezetimibe (Zetia), approved in 2002, inhibits the absorption of cholesterol in the intestine and is indicated to reduce LDL-cholesterol levels. Vytorin, the combination product approved in 2004, is indicated to reduce LDL-cholesterol levels.

Recently, FDA obtained preliminary results from the SEAS trial. This clinical trial tested whether lowering LDL-cholesterol with Vytorin would reduce the risk of major cardiovascular events, including aortic valve replacement, congestive heart failure, and ischemic cardiovascular events in individuals with aortic stenosis (a tight heart valve). A lower overall cardiovascular risk was not found with Vytorin. However, there was an additional observation that a larger percentage of subjects treated with Vytorin were diagnosed with and died from all types of cancer combined (including skin cancer) when compared to placebo during the 5-year study.

Interim data from two large ongoing cardiovascular trials of Vytorin – the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) – show no increased risk of cancer with the combination of simvastatin plus ezetimibe. The SHARP trial is expected to be completed in 2010. The IMPROVE-IT trial is scheduled for completion around 2012. Safety data from both of these trials are being evaluated on a regular basis by independent data safety monitoring boards. FDA has determined that, to date, these findings in the SEAS trial plus the interim data from ongoing trials should not prompt patients to stop taking Vytorin or any other cholesterol lowering drug.

FDA is aware of previous reports suggesting a link between low on-treatment cholesterol levels and an increased risk of cancer. A 2007 pooled analysis of 16 studies with 23 statin drug arms, published in the *Journal of the American College of Cardiology*, reported an association between the level of LDL-cholesterol achieved and incident cancer in patients receiving a statin.

However, most large prospective studies of statin drugs have reported no difference in cancer incidence between the active and placebo arms. For simvastatin, the Heart Protection Study randomized 20,000 patients to a daily dose of simvastatin 40 mg or placebo for up to 5 years. The incidence rate for cancer was 7.9% in the simvastatin group and 7.8% in the placebo group, and the deaths from cancer occurred at similar rates in both groups.

FDA anticipates receiving a final SEAS study report from the sponsors in about 3 months. Once FDA receives the final study report, it will likely take 6 months to fully evaluate the clinical trial data and other relevant information. As soon as this review is complete, FDA will communicate our conclusions and recommendations to the public.

An elevated LDL-cholesterol level is an established risk factor for heart disease and lowering cholesterol reduces the risk of death from heart disease and stroke. Patients should not stop taking Vytorin or other cholesterol lowering medications and should talk to their doctor if they have questions about whether to continue to take the medication. Until further information is available, healthcare professionals and caregivers should continue to monitor patients taking Vytorin as outlined in the prescribing information.

The FDA urges both healthcare professionals and patients to report side effects from the use of Vytorin to the FDA's MedWatch Adverse Event Reporting program

- on-line at www.fda.gov/medwatch/report.htm
- by returning the postage-paid FDA form 3500, available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787
- faxing the form to 1-800-FDA-0178
- by phone at 1-800-332-1088

References

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Date created: August 21, 2008

Information for Healthcare Professionals
Exenatide (marketed as Byetta)

Update 8/18/2008: Since issuing Information for Healthcare Professionals in October 2007, FDA has received reports of 6 cases of hemorrhagic or necrotizing pancreatitis in patients taking Byetta. Byetta is a medicine given by subcutaneous injection to help treat adults with type 2 diabetes. Of the 6 cases of hemorrhagic or necrotizing pancreatitis, all patients required hospitalization, two patients died and four patients were recovering at time of reporting. Byetta was discontinued in all 6 cases.

Byetta and other potentially suspect drugs should be promptly discontinued if pancreatitis is suspected. There are no known patient characteristics which determine when pancreatitis associated with Byetta will be complicated by the hemorrhagic or necrotizing forms of this condition. If pancreatitis is confirmed, initiate appropriate treatment and carefully monitor the patient until recovery. Byetta should not be restarted. Consider antidiabetic therapies other than Byetta in patients with a history of pancreatitis.

FDA is working with the maker of Byetta, Amylin Pharmaceuticals, Inc., to add stronger and more prominent warnings in the product label about the risk of acute hemorrhagic or necrotizing pancreatitis.

The prior FDA ALERT on the topic of acute pancreatitis in patients taking Byetta is shown below.

FDA ALERT [10/2007]: FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients taking Byetta, a drug used to treat adults with type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases.

Healthcare professionals should instruct patients taking Byetta to seek prompt medical care if they experience unexplained persistent severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.

FDA has asked and the maker of Byetta, Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA is not advising practitioners to discontinue prescribing the product. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

The Byetta full prescribing information will include new information in the PRECAUTIONS section about the potential for acute pancreatitis in patients taking Byetta.

Recommendations and Considerations

- **Healthcare providers should be alert to the signs and symptoms of acute pancreatitis.** Symptoms include persistent severe abdominal pain that can radiate to the back and may be accompanied by nausea and vomiting. Acute pancreatitis is typically confirmed by the presence of elevated levels of serum amylase and/or lipase and characteristic findings by radiological imaging.

- **Discontinue Byetta if pancreatitis is suspected.** If pancreatitis is confirmed, do not restart Byetta unless an alternative etiology for the pancreatitis is identified.

Information for the patient: *Physicians who prescribe Byetta should discuss with their patients:*

Byetta is a medicine given by injection to help treat adults with type 2 diabetes. Commonly reported side effects of Byetta include nausea, vomiting, diarrhea, indigestion and upper abdominal discomfort. However, the presence of unexplained, severe abdominal pain, with or without nausea and vomiting, raises the suspicion of acute pancreatitis, a potentially serious condition that requires prompt medical attention. Therefore, patients taking Byetta should promptly seek medical care if they experience unexplained severe abdominal pain with or without nausea and vomiting.

Background Information and Data

FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients treated with Byetta. Twenty-seven of the 30 patients had at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridemia, and alcohol use. In six patients the symptoms of pancreatitis began or worsened soon after the dose of Byetta was increased from 5 micrograms twice daily to 10 micrograms twice daily. Twenty-one patients were hospitalized. There were no reports of hemorrhagic or necrotizing pancreatitis. However, five patients developed serious complications including dehydration and renal failure; suspected ileus; phlegmon; and ascites. Twenty-two of the 30 reports indicated that the patients improved after discontinuing Byetta.

Details in three reports indicated that the symptoms of acute pancreatitis returned when Byetta was restarted. Nausea and vomiting returned in two patients when Byetta was restarted. In a third patient, abdominal pain returned when Byetta was restarted and abated after Byetta was permanently discontinued.

FDA has asked and the maker of Byetta, Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the Precautions section of the product label.

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Date created: October 16, 2007, updated August 18, 2008

2008 Safety Alert: Fentanyl Transdermal System Patches

The following information is from Watson Pharmaceuticals, Inc. Contact the company for a copy of any referenced enclosures.

Watson Announces Limited Recall Of Fentanyl

CORONA, CA - August 8, 2008 - Watson Pharmaceuticals, Inc., a leading specialty pharmaceutical company, announced today that one lot of 75 mcg/hr Fentanyl Transdermal System patches sold in the United States is being voluntarily recalled from wholesalers and pharmacies. The recalled patches are from Lot Number 92461850, have expiration dates of August 31, 2009 and were manufactured by Watson Laboratories, Inc. The affected lot of Fentanyl Transdermal System patches was shipped to customers between January 30, 2008 and March 19, 2008. No other strengths or lots were affected and the Company does not anticipate any product shortages as a result of this recall. The Company has notified the U.S. Food and Drug Administration (FDA) of the recall.

A small number of patches leaking fentanyl gel have been detected in this lot, potentially exposing patients or caregivers directly to fentanyl gel. Fentanyl patches that are leaking should not be used. No injuries have been reported in connection with the recalled lot. However, exposure to fentanyl gel may lead to serious adverse events, including respiratory depression and possible overdose, which may be fatal.

Anyone who has 75 mcg/hr Fentanyl Transdermal System patches should check the box or foil pouch for the lot number and expiration date to see if they have patches that are being recalled. Affected patches should not be handled directly. Anyone with 75 mcg/hr Fentanyl Transdermal System patches being recalled should call 888-667-1508, Monday through Friday, 8:00 a.m.-5:00 p.m. EDT, for instructions on how to return affected product.

Patients using fentanyl patches who have medical questions should contact their health-care providers.

Any adverse reactions experienced with the use of this product, and/or quality problems should also be reported to the FDA's MedWatch Program by phone at 1-800-FDA-1088, by Fax at 1-800-FDA-0178, by mail at MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch website at www.fda.gov/medwatch.

Fentanyl Transdermal System CII is indicated for the management of persistent, moderate to severe chronic pain that requires continuous, around the clock opioid administration for an extended period of time and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate release opioids.

Anyone who comes in contact with fentanyl gel should thoroughly rinse exposed skin with large amounts of water only; do not use soap. Immediately dispose of affected patches that may be damaged or compromised in any way by flushing them down the toilet, using caution not to handle them directly. Damaged and/or compromised patches that have leaked gel will not provide effective pain relief.

About Watson Pharmaceuticals, Inc.

Watson Pharmaceuticals, Inc., headquartered in Corona, CA, is a leading specialty pharmaceutical company that develops, manufactures, markets, sells and distributes brand and generic pharmaceutical products. Watson pursues a growth strategy combining internal product development, strategic alliances and collaborations and synergistic acquisitions of products and businesses.

For press releases and other company information, visit Watson Pharmaceuticals' Web site at http://www.watson.com.

Forward-Looking Statement

Any statements contained in this press release that refer to future events or other non-historical facts are forward-looking statements that reflect Watson's current perspective of existing trends and information as of the date of this release. Except as expressly required by law, Watson disclaims any intent or obligation to update these forward-looking statements. Actual results may differ materially from Watson's current expectations depending upon a number of factors affecting Watson's business. These factors include, among others, the impact of competitive products and pricing; market acceptance of and continued demand for Watson's products, including its Fentanyl Transdermal System; risks related to our successful compliance with extensive, costly, complex, and evolving governmental regulations and restrictions; the difficulty of predicting the timing or outcome of FDA or other regulatory agency approvals or actions; difficulties or delays in manufacturing; and other risks and uncertainties detailed in Watson's periodic public filings with the Securities and Exchange Commission, including but not limited to Watson's Annual Report on Form 10-K for the year ended December 31, 2007.

Information for Healthcare Professionals
Simvastatin (marketed as Zocor and generics), Ezetimibe/Simvastatin (marketed as Vytorin), Niacin extended-release /Simvastatin (marketed as Simcor), used with Amiodarone (Cordarone, Pacerone)

FDA ALERT [08/08/2008]: The FDA is notifying the public of the risk of a rare condition of muscle injury called rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone. This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. A revision of the simvastatin labeling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily. However, the FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin, particularly with simvastatin doses greater than 20 mg daily. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

This information reflects FDA's current analysis of data available to FDA concerning these drugs. FDA intends to update this sheet when additional information or analyses become available.

To report any unexpected adverse or serious events associated with the use of these drugs, please contact the FDA MedWatch program and complete a form on line at http://www.fda.gov/medwatch/report/hcp.htm or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.

Recommendations and Information for Healthcare Professionals to Consider When Prescribing Simvastatin to Patients Taking Amiodarone:

- Healthcare professionals, who prescribe simvastatin or simvastatin-containing medications (Simcor, Zocor, Vytorin), should be aware that patients taking amiodarone should not take more than 20 mg per day of simvastatin. Doses higher than 20 mg each day increase the risk of rhabdomyolysis, a rare condition of muscle injury.

- As with other statins, the risk of rhabdomyolysis is dose related. All patients, starting therapy with simvastatin or whose dose of simvastatin is being increased, should be advised of the risk of rhabdomyolysis and told to report promptly any unexplained muscle pain, tenderness or weakness.

- The risk of rhabdomyolysis is increased when higher doses of simvastatin are administered with amiodarone. The precise mechanism is unknown, but is related to the fact that amiodarone inhibits the cytochrome P450 3A4 (CYP3A4) enzyme. This is the same enzyme that metabolizes simvastatin. Prescribers should consider use of another statin for patients taking amiodarone, or initiating amiodarone therapy, who require simvastatin doses greater than 20 mg daily to meet their lipid goals.

- Rhabdomyolysis has been reported with all statins. Predisposing risk factors for rhabdomyolysis include advanced age (≥65 years), uncontrolled hypothyroidism, and renal impairment.

Information for Healthcare Professionals to Consider When Counseling Patients:

- Amiodarone is used to control a heart rhythm problem and simvastatin is used to lower cholesterol.
- Simvastatin interacts with amiodarone and can cause a rare muscle injury condition called rhabdomyolysis. This condition can lead to kidney failure and possibly death.
- If you are taking amiodarone and a cholesterol-lowering drug product containing simvastatin, you should not take more than 20 mg of simvastatin each day because your risk of developing rhabdomyolysis increases.
- If you are starting therapy with simvastatin, or your dose of simvastatin is being increased, contact your doctor immediately if you experience symptoms of unexplained muscle injury, such as muscle cramps, pain, tenderness, stiffness or spasm.
- Tell your doctor about all the medications you are taking.

Data Summary

Simvastatin is a member of the class of drugs known as HMG-CoA reductase inhibitors or "statins". Simvastatin has demonstrated benefit in lowering cholesterol and reducing some cardiac risks. Amiodarone is an antiarrhythmic drug approved only for controlling life-threatening recurrent ventricular arrhythmias.

The simvastatin prescribing information was updated in May 2002, to warn of an increased risk of rhabdomyolysis when amiodarone is used with simvastatin at doses greater than 20 mg daily. Despite the added warning to the prescribing information of simvastatin drug products, the FDA continues to receive serious reports of rhabdomyolysis when amiodarone is used with simvastatin, particularly with simvastatin doses greater than 20 mg daily.

Compared to other statins, the risk of rhabdomyolysis is more pronounced when simvastatin is administered with amiodarone. All statins carry a potential risk of rhabdomyolysis, whether or not they are administered with amiodarone.

The FDA does not have data on how varying the dose of amiodarone in patients taking simvastatin affects the risk of developing rhabdomyolysis.

The FDA and the manufacturer are revising the Cordarone (amiodarone) prescribing information to warn of an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses exceeding 20 mg daily.

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Date created: August 8, 2008