Drug Utilization Review Board

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

The University of Oklahoma
Health Sciences Center
COLLEGE OF PHARMACY
PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Chris Le, Pharm.D.

SUBJECT: Online Packet Contents

DATE: October 1, 2013

NOTE: The DUR Board will not meet.

Enclosed are the following items:

DUR Board Recommendations Memorandum from September 11, 2013 – See Appendix A.

MCAU & SoonerCare Atypical Rx Program Update – See Appendix B

Annual Review of Kalydeco™ (Ivacaftor) – See Appendix C.

Annual Review of Makena® (17-Hydroxyprogesterone Caproate) – See Appendix D.

Annual Review of Cinryze® and Berinert® (C1 Esterase Inhibitors), Kalbitor® (Ecallentide), and Firazyr® (Icatibant) – See Appendix E.

Annual Review of Xiaflex® (Collagenase Clostridium Histolyticum) – See Appendix F.

Annual Review of Xgeva® (Denosumab) – See Appendix G.

FDA and DEA Updates – See Appendix H.

Future Business: Annual Reviews - Botulinum Toxins, Antihypertensive Medications, Glaucoma Medications, Nasal Allergy Medications, Pediculicides, Prenatal Vitamins

Appendix A

The University of Oklahoma
Health Sciences Center
COLLEGE OF PHARMACY
PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: September 11, 2013

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

From: Bethany Holderread, Pharm.D.
Clinical Pharmacist
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of September 11, 2013

Recommendation 1: Vote to Prior Authorize Tysabri® (Natalizumab)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends medical and pharmacy prior authorization of Tysabri® (natalizumab).

Consideration will be based on **all** of the following criteria:

1. An FDA approved diagnosis of multiple sclerosis or Crohn's disease; **AND**
2. Treatment with at least **two** different first line therapeutic categories for multiple sclerosis or Crohn's disease that have failed to yield an adequate clinical response, or a patient specific, clinically significant reason why the member cannot use all available first and second line alternatives; **AND**
3. Prescriber, infusion center, and member must enroll in the TOUCH Prescribing Program.

Recommendation 2: Vote to Prior Authorize Diclegis® (Doxylamine/Pyridoxine)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends prior authorization of Diclegis® (doxylamine/pyridoxine).

Consideration will be based on **all** of the following criteria:

1. An FDA approved diagnosis of nausea and vomiting associated with pregnancy; **AND**
2. Trials with at least **two** non-pharmacologic therapies that have failed to relieve nausea and vomiting; **AND**
3. Trials with at least **three** prescription medications that have failed to relieve nausea and vomiting (must include a trial of ondansetron); **AND**
4. A patient-specific, clinically significant reason why member cannot use OTC doxylamine and OTC Vitamin B-6 (pyridoxine).

Recommendation 3: Vote to Prior Authorize Quillivant XR™ (Methylphenidate Extended Release) Oral Suspension and Update the ADHD Prior Authorization Category

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of Quillivant XR™ to the ADHD Product Based Prior Authorization Category, as well as the following changes to the current criteria and tier structure.

TIER 1	TIER 2	TIER 3	SPECIAL PA
AMPHETAMINE			Desoxyn® tablets Dexedrine® tablets Dextroamphetamine tablets *(generic Dexedrine®)* Dexedrine Spansules® caps Dextroamphetamine ER capsules *(generic Dexedrine Spansules®)* ProCentra™ solution Methylin® Chewable Tablets Methylin® Solution Methylphenidate Solution *(generic Methylin®)* Provigil® (modafinil tablets) Modafinil tablets *(generic Provigil®)* Nuvigil® (armodafinil tablets) Xyrem® (sodium oxybate soln)
Short-Acting Adderall® tablets Amphetamine/ Dextroamphetamine tablets *(generic Adderall®)*			
Long-Acting **Lowest Net Cost Long-Acting Product*	***Long-Acting*** *Intermediate Net Cost Range Product(s)*	***Long-Acting*** Adderall XR® capsules Amphetamine/Dextroamphetamine ER capsules *(generic Adderall XR®)* Vyvanse® capsules	
METHYLPHENIDATE			
Short-Acting Ritalin® tablets Methylphenidate tablets *(generic Ritalin®)* Focalin® tablets Dexmethylphenidate tablets *(generic Focalin®)* Methylin® tablets Methylphenidate tablets *(generic Methylin®)*			
Long-Acting Methylin ER® tablets Methylphenidate ER tablets *(generic Methylin ER®)* Ritalin SR® tablets Methylphenidate SR tablets *(generic Ritalin SR®)* Metadate ER® tablets Methylphenidate ER tablets *(generic Metadate ER®)* **Lowest Net Cost Long-Acting Product*	***Long-Acting*** *Intermediate Net Cost Range Product(s)*	***Long-Acting*** Concerta® tablets Methylphenidate ER tablets *(generic Concerta®)* Focalin XR® capsules Metadate CD® capsules Methylphenidate CD capsules *(generic Metadate CD®)* Ritalin LA® capsules Methylphenidate LA capsules *(generic Ritalin LA®)* Daytrana™ patches Quillivant XR™ suspension	
NON-STIMULANTS∞			
	Lowest Net Cost Product	Kapvay® (clonidine ER tablets) Intuniv® (guanfacine ER tablets) Strattera® (atomoxetine caps)	

*Final Tier 1 category must contain a long-acting capsule.
∞ May Rebate to Tier-2 Status only.

Tier 2 Prior Authorization Approval Criteria:

1. FDA approved diagnosis; and
2. Trials with at least one long-acting Tier one drug from each category (one amphetamine and one methylphenidate):
    a. Trials should have been within the last 180 days; and
    b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
    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.

Tier 3 Prior Authorization Approval Criteria:

1. FDA approved diagnosis; and
2. Trials with at least one long-acting Tier one drug from each category (one amphetamine and one methylphenidate); and
3. Trials with at least two Tier 2 medications that did not yield adequate response:
    a. Trials should have been within the last 365 days; and
    b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
    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.
4. A clinical exception may apply for special formulation products when there is a patient-specific, clinically significant reason why member cannot use the available long acting capsule formulation.

Special Prior Authorization Approval Criteria:

1. **Desoxyn®, Dexedrine®, Dexedrine Spansules®, and ProCentra™ Solution** Criteria:
    a. Covered diagnosis; and
    b. A patient-specific, clinically significant reason why member cannot use all other available stimulant medications.
2. **Methylin® Chewable Tablets & Solution Criteria:**
    a. FDA approved diagnosis; and
    b. A patient-specific, clinically significant reason why member cannot use all other available formulations of long acting stimulant medications that can be used for members who cannot swallow capsules/tablets.
3. **Provigil®, Nuvigil®, and Xyrem® Criteria:**
    a. FDA approved diagnosis.
    b. Use of Provigil®, Nuvigil®, or Xyrem® requires a patient-specific, clinically significant reason why member cannot use stimulant medications to improve wakefulness during the daytime.
    c. Use of Xyrem® requires recent trials with Tier 1 and Tier 2 stimulants from different chemical categories, and trials with both Provigil® and

Nuvigil® within the past 6 months, unless contraindicated, that did not yield adequate results.

d. The diagnosis of obstructive sleep apnea requires concurrent treatment for the obstructive sleep apnea.
e. The diagnosis of shift work sleep disorder requires the member's work schedule to be included with the petition.

Additional Criteria:

1. Doses exceeding 1.5 times the FDA maximum are not covered.
2. Prior Authorization is required for all tiers for members greater than 20 years of age and for members 0-4 years of age. All prior authorization requests for members under the age of 5 years must be reviewed by an OHCA contracted psychiatrist.
3. Please note, members currently stabilized on ADHD medications in the previous 30 days will be grandfathered.

Recommendation 4: Vote to Update the Atypical Antipsychotics Product Based Prior Authorization Criteria

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes to the Atypical Antipsychotics Product Based Prior Authorization Category as shown below. The final tier status of each branded product will apply across all available formulations of the product line.

Atypical Antipsychotics*

Tier 1	Tier 2	Tier 3†
risperidone **(Risperdal®, Risperdal Consta®)** olanzapine **(Zyprexa®)** quetiapine **(Seroquel®)** ziprasidone **(Geodon®)** clozapine **(Clozaril®)**¥	Supplemental Rebated Products	aripiprazole **(Abilify®, Abilify Maintena™)** asenapine **(Saphris®)** clozapine **(Fazaclo®)** iloperidone **(Fanapt™)** lurasidone **(Latuda®)** olanzapine/fluoxetine **(Symbyax®)** paliperidone **(Invega®, Invega Sustenna®)** quetiapine ER **(Seroquel XR®)**

* **Mandatory Generic Plan Applies**
† **May be rebated to Tier 2 status only**
¥ **Does not count toward a tier-1 trial**

Approval Criteria for Tier 2 Medication:

1. Trials of **two** Tier 1 products (not including clozapine), at least 14 days in duration each, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.

Approval Criteria for Tier 3 Medication:

1. Trials of **two** Tier 1 products (not including clozapine), at least 14 days in duration each, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects; and
2. Trials of **two** Tier 2 medications, at least 14 days in duration each, titrated to recommended dose, that did not yield adequate response or resulted in intolerable adverse effects.
3. A manual prior authorization may be submitted for consideration of a Tier-3 product when the member has had at least 4 trials of Tier-1 and Tier-2 products (2 trials must be from Tier-1) that did not yield an adequate response or resulted in intolerable adverse effects.

Approval Criteria for Atypical Antipsychotics as Adjunctive Treatment for Depression:

1. For Abilify® (aripiprazole), Seroquel XR® (quetiapine extended release), or Symbyax® (olanzapine/fluoxetine): a diagnosis of depression requires current use of an antidepressant, and previous trials with at least two other antidepressants from both categories (an SSRI and a dual acting antidepressant) that did not yield adequate response. Tier structure applies.

Clinical Exceptions:

1. Members currently stabilized on a higher tiered medication defined by paid claim(s) for the higher tiered medication in the past 90 days will be approved.
2. Members being released from a hospital and stabilized on a higher tiered medication will be approved.
3. Approvals will be granted for members with clinical conditions for which lower tiered drugs are contraindicated.
4. Approvals will be granted for members whose current regimen includes drugs known to adversely interact with all lowered tiered drugs.
5. Lurasidone (Latuda®) may be approved for pregnant women with appropriate diagnosis.

Second Opinion Process for Children 0 - 4 Years of Age

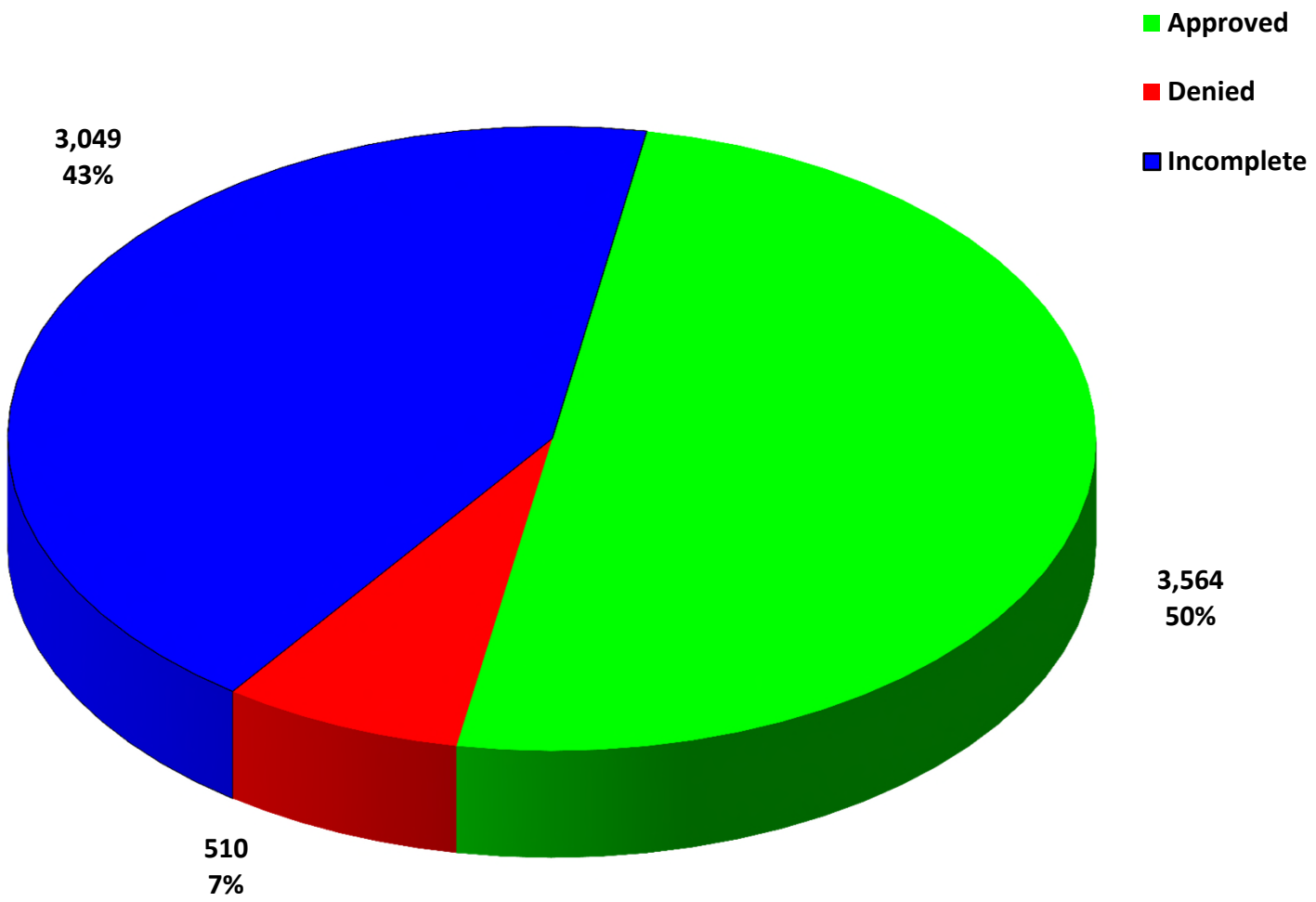
Children less than 5 years of age will require a "second opinion" prior authorization to be reviewed by an OHCA-contracted child psychiatrist.

Educational Initiative for Inpatient Behavioral Health Providers

Due to the cost of inpatient psychiatric stays, the College of Pharmacy does not recommend removing the inpatient stabilization approval criteria at this time. However, COP and OHCA plan to work closely with the OHCA Inpatient Behavioral Health providers' group, which meets regularly at the agency, to educate them about the potential benefits of adopting the OHCA preferred drugs as their formulary products.

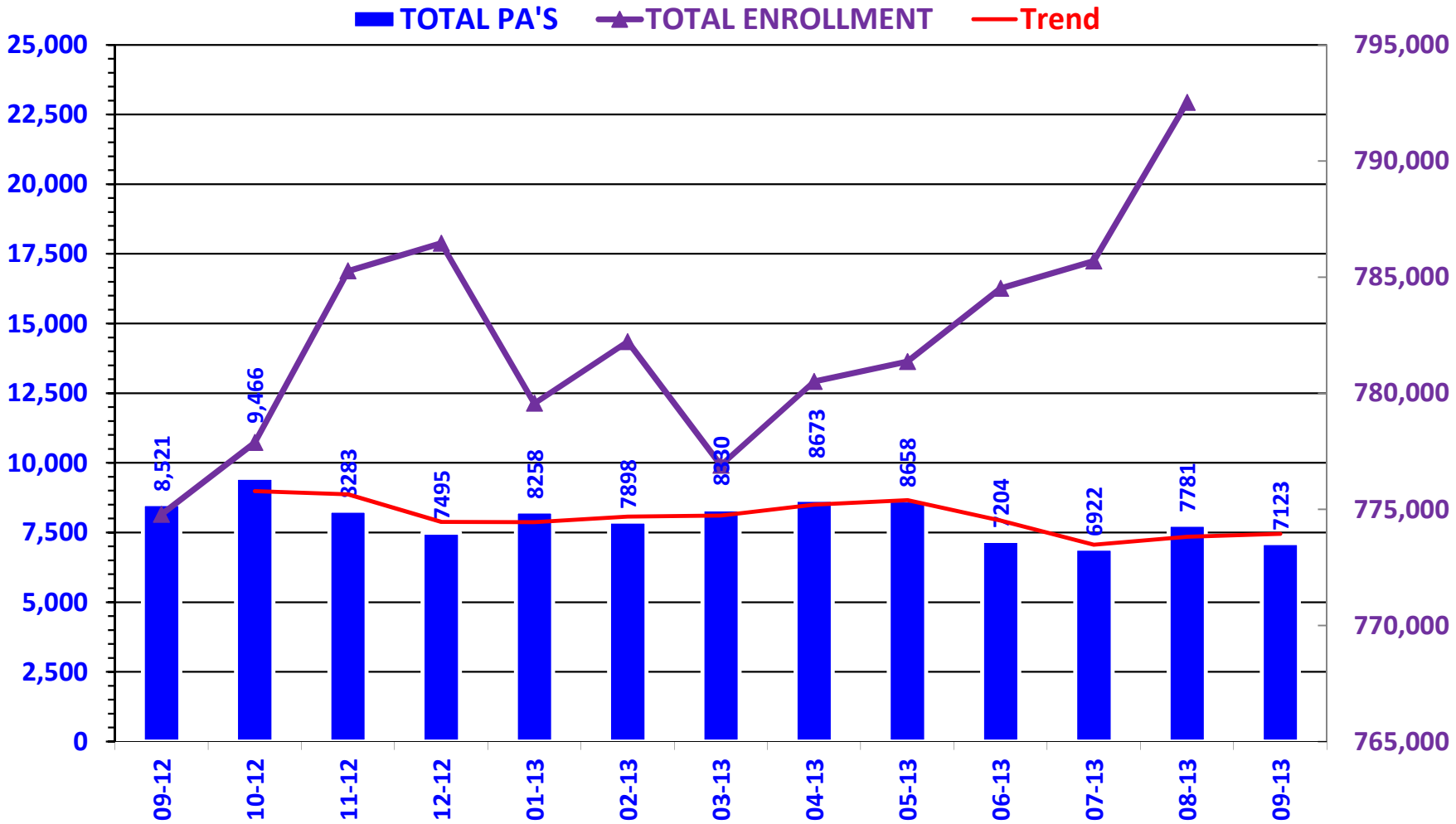
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: SEPTEMBER 2013



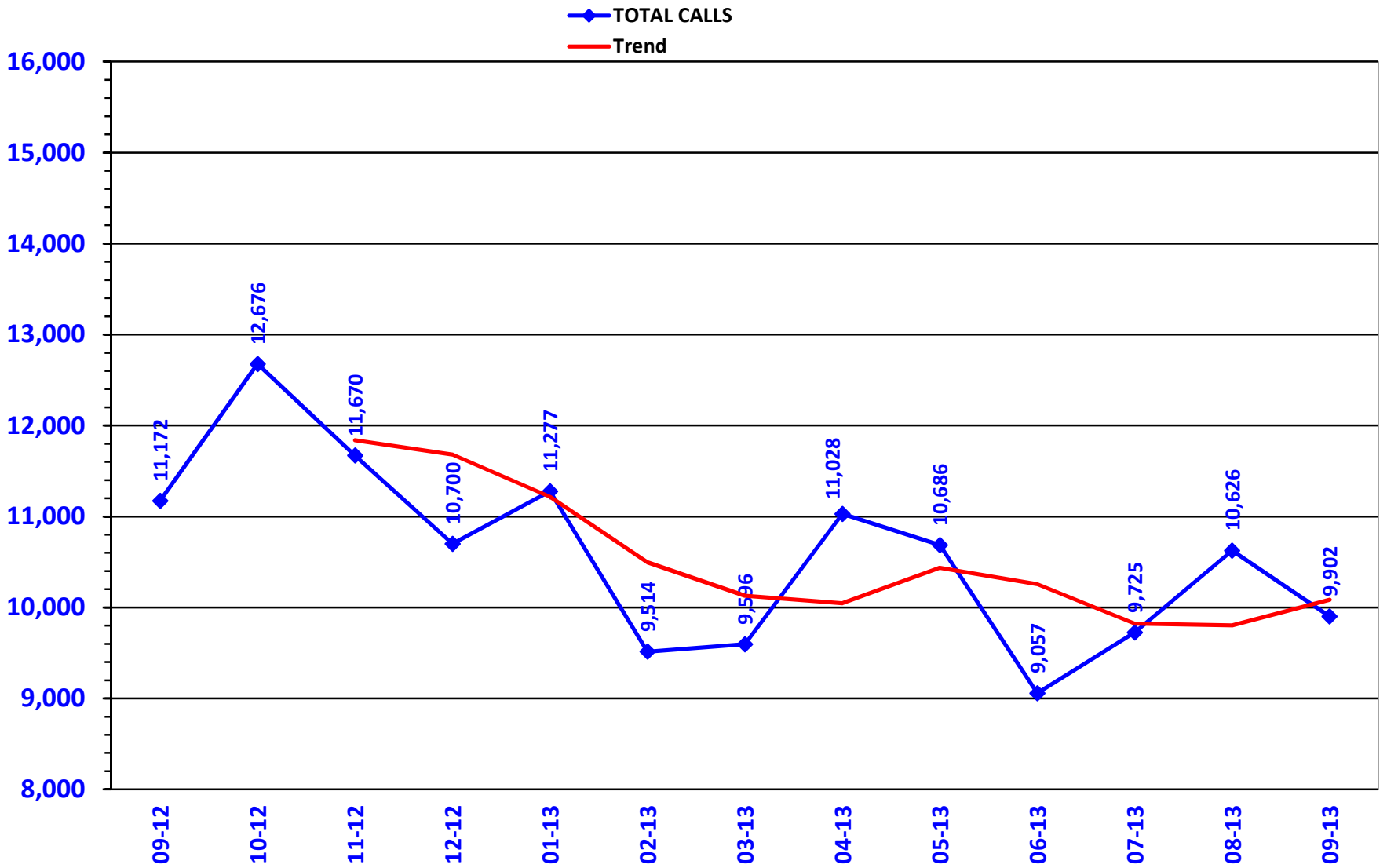
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: SEPTEMBER 2012- SEPTEMBER 2013



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
SEPTEMBER 2012- SEPTEMBER 2013



Prior Authorization Activity

9/1/2013 Through 9/30/2013

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	406	168	6	232	353
Analgesic, Narcotic	369	193	16	160	229
Angiotensin Receptor Antagonist	33	5	3	25	357
Antiasthma	244	129	7	108	272
Antibiotic	30	4	1	25	30
Anticoagulant	60	44	0	16	320
Anticonvulsant	98	49	0	49	332
Antidepressant	241	81	24	136	338
Antidiabetic	124	55	4	65	336
Antihistamine	174	137	2	35	347
Antihyperlipidemic	12	2	2	8	360
Antimigraine	73	24	9	40	334
Antiplatelet	16	15	0	1	338
Antiulcers	243	65	46	132	126
Anxiolytic	89	58	1	30	216
Atypical Antipsychotics	421	271	11	139	336
Biologics	38	19	2	17	306
Bladder Control	61	13	6	42	304
Botox	32	18	8	6	362
Calcium Channel Blockers	11	7	1	3	243
Cardiovascular	26	11	0	15	313
Chronic Obstructive Pulmonary Disease	17	6	1	10	359
Dermatological	106	16	35	55	104
Endocrine & Metabolic Drugs	64	45	2	17	136
Erythropoietin Stimulating Agents	14	10	0	4	105
Fibromyalgia	161	36	12	113	340
Gastrointestinal Agents	138	42	12	84	123
Genitourinary Agents	12	6	0	6	26
Glaucoma	11	5	0	6	359
Growth Hormones	60	41	9	10	165
HFA Rescue Inhalers	63	22	3	38	331
Insomnia	50	8	8	34	176
Multiple Sclerosis	18	13	0	5	255
Muscle Relaxant	124	25	34	65	51
Nasal Allergy	107	11	32	64	137
Neurological Agents	72	47	2	23	348
Nsaids	158	28	14	116	246
Ocular Allergy	51	14	3	34	153
Ophthalmic	27	8	0	19	18
Other*	174	31	29	114	193
Otic Antibiotic	37	11	0	26	14
Pediculicide	87	30	16	41	18
Prenatal Vitamins	11	0	1	10	0
Statins	75	23	9	43	359
Stimulant	527	308	18	201	319
Suboxone/Subutex	188	143	5	40	74
Synagis	12	0	1	11	0
Testosterone	72	22	4	46	349
Topical Antibiotic	13	2	1	10	222
Topical Antifungal	66	1	16	49	117
Topical Corticosteroids	178	14	27	137	216
Vitamin	46	14	21	11	313
Pharmacotherapy	220	128	7	85	151
Emergency PAs	3	3	0	0	
Total	**5,763**	**2,481**	**471**	**2,811**	

* Includes any therapeutic category with less than 10 prior authorizations for the month.

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Overrides					
Brand	64	51	0	13	303
Cumulative Early Refill	23	23	0	0	62
Dosage Change	370	337	5	28	6
High Dose	2	2	0	0	266
Ingredient Duplication	11	9	0	2	5
Lost/Broken Rx	75	73	0	2	4
Nursing Home Issue	86	83	0	3	5
Other	32	28	0	4	44
Quantity vs. Days SupplQu	1	0	0	1	0
Quantity vs. Days Supply	10	0	2	8	0
Quantity vs. Days Supply	688	461	25	202	262
Stolen	5	5	0	0	3
Temporary Unlock	28	19	9	0	38
Third Brand Request	52	24	7	21	40
Wrong D.S. on Previous Rx	1	0	0	1	0
Overrides Total	**1,414**	**1,092**	**46**	**276**	
Total Regular PAs + Overrides	**7,177**	**3,573**	**517**	**3,087**	

Denial Reasons	
Unable to verify required trials.	2,606
Does not meet established criteria.	520
Lack required information to process request.	472

Other PA Activity	
Duplicate Requests	436
Letters	3,096
No Process	58
Changes to existing PAs	471
Partials	797

* Includes any therapeutic category with less than 10 prior authorizations for the month.

SoonerCare Atypical RX Program Update

Oklahoma Health Care Authority
October 2013

Physician Response to June Mailing: Dosing and Diagnosis in Pediatric Members Receiving an Atypical Antipsychotic

Approximately 812 prescribers for children were listed on paid pharmacy claims for atypical antipsychotics in the 12 months prior to the report date. A total of 5,864 unduplicated members with atypical antipsychotic claims were reviewed for nonstandard dosing or lack of a strong diagnosis. Nonstandard dosing was determined by atypical antipsychotic claims with dosing greater than or equal to 1.5 times the FDA maximum dose. Inclusion based on diagnosis was determined by the absence of a diagnosis with a strong indication for prescribing an antipsychotic medication during the 12 month review period.

There were 95 members flagged for nonstandard dosing and 4,195 members flagged for lack of strong diagnoses. 553 members were randomly chosen for inclusion in the mailing. Packets were mailed to 200 prescribers. The packets included information regarding standard dosing of atypical antipsychotics and diagnoses consistent with a strong indication for antipsychotic use. The packets also contained patient specific prescription claim information with an optional individual member response page which allows the prescriber to provide feedback. Because some prescribers had multiple members, the maximum number of members included in a single packet was 10.

Summary of Mailing

Letters/Physicians	Count
Total Letters Mailed	200
Members	
Total Members Included	553
Total Responses Received	222

Prescriber Response Summary

Q#	Response	Total*
Q1	Possible billing error – Not my patient.	3
Q2	I am no longer seeing this patient.	11
Q3	Medication has been changed prior to date of review letter.	16
Q4	I was unaware of this situation and will consider making appropriate changes in therapy.	4
Q5	I am aware of this situation and will plan to continue monitoring this therapy.	144
Q6	I am continuing this medication from an original psychiatric prescription.	108
Q7	Other, comments.	125
	I am placing the Patient Detail Report in the patient's medical record	53

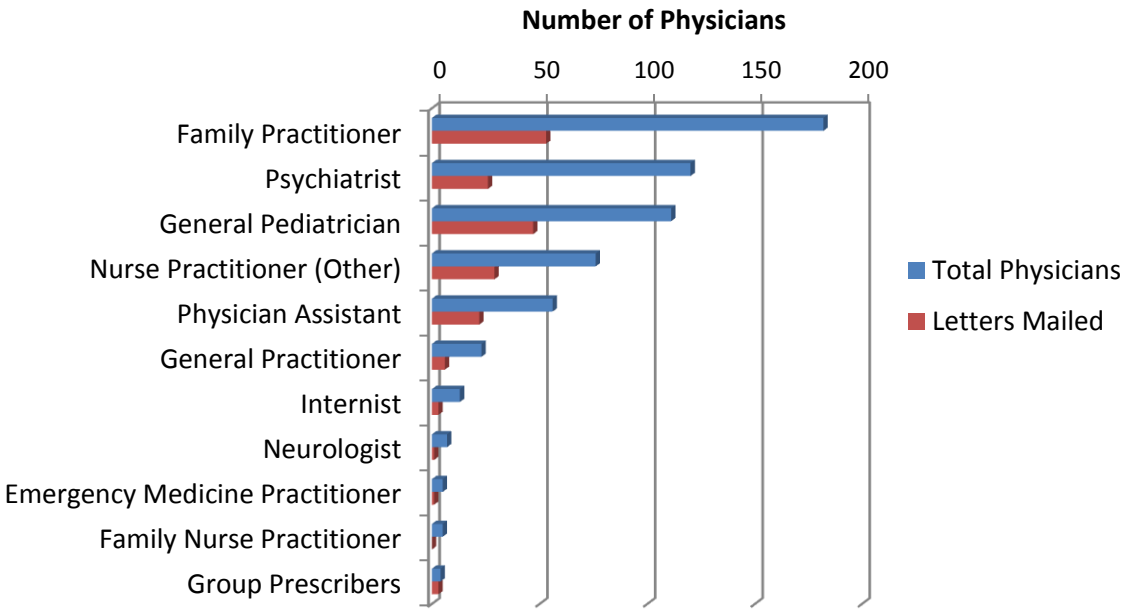
*Members can be included in multiple categories.

Summary of Additional Comments Provided

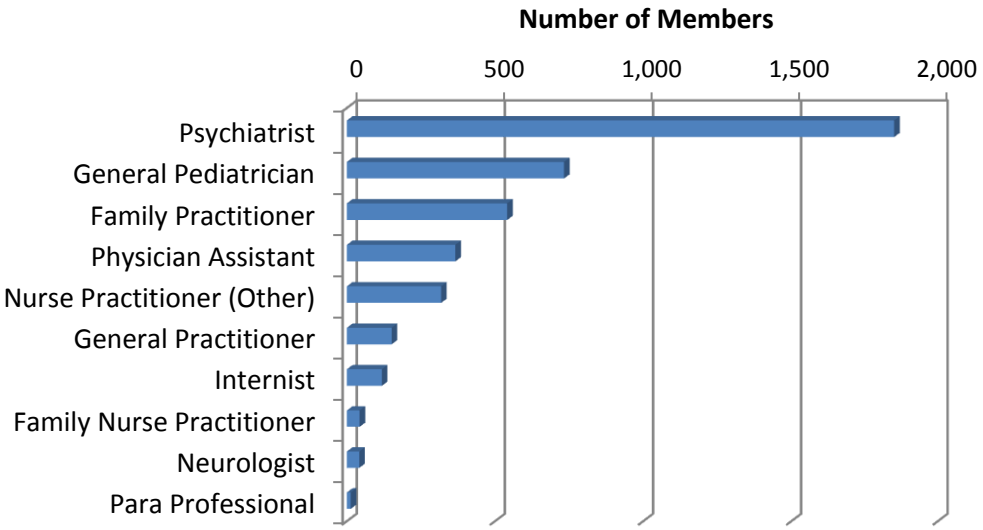
Comment Category	Total*
Patient specific information provided	58
I am aware and will continue monitoring therapy	27
Continuing medications from previous prescriber	27
I have referred this patient to another prescriber	16
Patient therapy is being followed by another prescriber	12
Medication has been discontinued	8
No longer my patient	8
Not my patient	5
I plan to discontinue this medication gradually	3
Patient has missed appointments/reports non-compliance/dropped out of treatment	2

*Members can be included in multiple categories, not all responses listed.

Total Physicians Versus Physicians Who Received a Letter by Prescriber Specialty



Top Ten Prescriber Specialties by Number of Members Included in Overall Review



Last Mailing –September 2013

The last mailing was processed in September and addressed poly-pharmacy for adult and pediatric members. For this project, poly-pharmacy was determined by claims for two or more atypical antipsychotic medications concurrently for 90 days or more. The review period was for six months and was prevalent in nature (not based on a new start of an atypical antipsychotic). Members were eligible for inclusion in the mailing if their claims history indicated concurrent use of two or more atypical antipsychotic medications. A total of 200 prescribers and 459 members were included in this mailing.

Appendix C

Fiscal Year 2013 Annual Review of Kalydeco™ (Ivacaftor)

Oklahoma Health Care Authority
October 2013

Current Prior Authorization Criteria

The prior authorization of Kalydeco™ (ivacaftor) was implemented in May 2012.
The current approval criteria are as follows:

1. FDA approved indication of cystic fibrosis with a G551D mutation in the CFTR gene detected by genetic testing.
2. Age of 6 years or older.
3. Quantity limit of two tablets per day, #60 tablets per 30 days will apply.
4. Initial approval will be for 6 months, after which time, compliance and information regarding efficacy, such as improvement in $FEV_{1,}$ will be required for continued approval.

Utilization of Kalydeco™

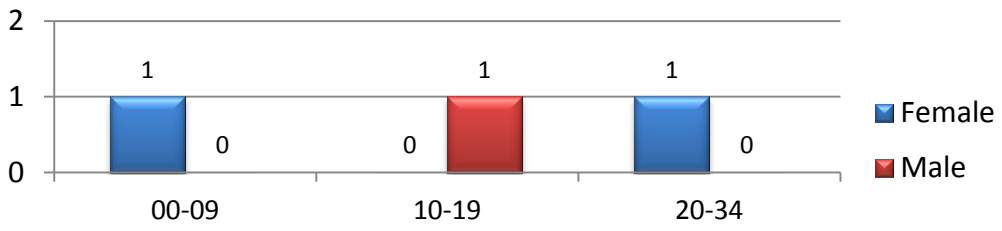
Comparison of Fiscal Years

Fiscal Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2012	3	13	$325,380.10	$25,029.24	$834.31	780	390
2013	3	24	$613,706.86	$25,571.12	$852.37	1,440	720
% Change	**0.00%**	**84.60%**	**88.60%**	**2.20%**	**2.20%**	**84.60%**	**84.60%**
Change	**0**	**11**	**$288,326.76**	**$541.88**	**$18.06**	**660**	**330**

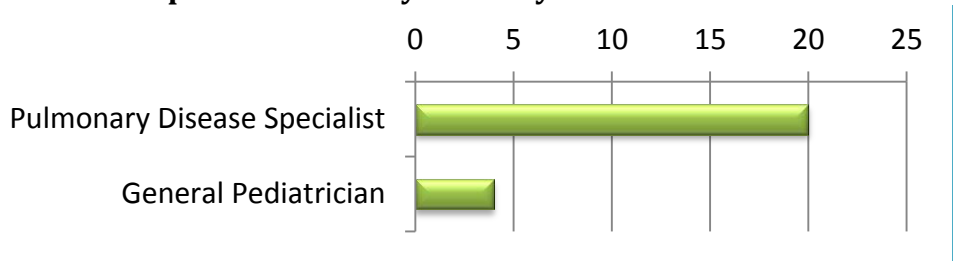
Utilization Details of Kalydeco™: FY 2013

Chemical Name	Brand Name	Claims	Members	Cost	Cost/Day
Ivacaftor	Kalydeco™	24	3	$613,706.86	$852.37

Demographics of Members Utilizing Kalydeco™: FY 2013



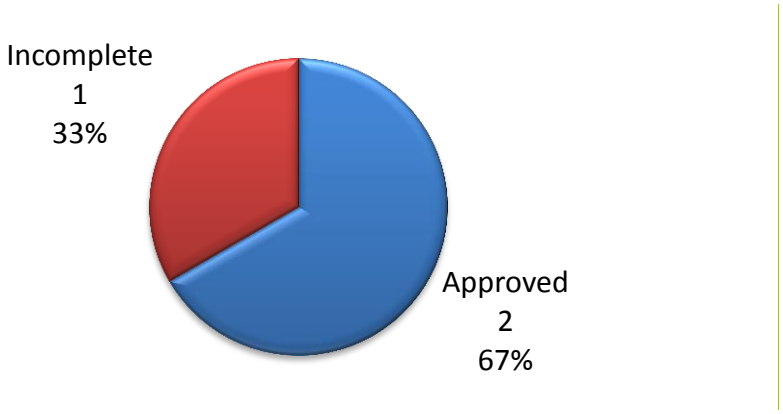
Prescriber Specialties of Kalydeco™ by Number of Claims: FY 2013



Prior Authorization of Kalydeco™

There were a total of 3 petitions submitted for this medication during fiscal year 2013. The following chart shows the status of the submitted petitions.

Status of Petitions for Kalydeco™: FY 2013



Market News and Update[1,2]

- Anticipated patent expiration of Kalydeco™- 12/2026
- Vertex Pharmaceuticals, Inc. (manufacturer of Kalydeco™) has three other medications in development for cystic fibrosis, currently in Phase 1, Phase 2, and Phase 3 Clinical Trials. These agents are evaluated as combination therapy with Kalydeco™ in cystic fibrosis patients who have two copies of the F508del-CFTR mutation.
- PTC Therapeutics Inc. has completed Phase 3 Clinical Trials which shows a lower decline in lung function and a lower rate in pulmonary exacerbations when Ataluren® (PTC 124) was compared to placebo. This Phase 3 trial has been extended to evaluate the long-term safety in cystic fibrosis patients who have a nonsense mutation.

Conclusion and Recommendations

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

[1] Cystic Fibrosis Foundation: Drug Development Pipeline. Available online at: http://www.cff.org/research/drugdevelopmentpipeline/. Last accessed 9/24/13.
[2] Vertex Pharmaceuticals, Inc.: Research & Development Pipeline. Available online at: http://www.vrtx.com/research-development/pipeline. Last accessed 9/24/13.

Appendix D

Fiscal Year 2013 Annual Review of Makena®
(17-Hydroxyprogesterone Caproate)

Oklahoma Health Care Authority
October 2013

Current Prior Authorization Criteria

Makena® (17-hydroxyprogesterone caproate) was approved by the FDA in February 2011, and was covered under the medical benefit for SoonerCare members. Medical prior authorization was implemented in January 2012. On September 1, 2012 coverage of Makena® was placed under the pharmacy benefit. The manufacturer, Ther-Rx, put into place a network of specialty pharmacies to distribute Makena®. Makena® is currently covered as a pharmacy-only benefit, and the current approval criteria are as follows:

1. Documented history of previous singleton spontaneous preterm delivery (SPTD) prior to 37 weeks gestation; and
2. Current singleton pregnancy; and
3. Gestational age between 16 weeks, 0 days and 20 weeks, 6 days of gestation.
4. Authorizations will be for once a week administration in an office setting through 36 weeks, 6 days of gestation.

Utilization of Makena®

Comparison of Fiscal Years: Generic Hydroxyprogesterone Caproate (Medical)

Fiscal Year	Members	Claims	Cost	Cost/Claim	Units
2012	160	795	$6,962.55	$8.76	810
2013	250	1575	$17,286.72	$10.98	1575
% Change	**56.25%**	**98.11%**	**148.28%**	**25.32%**	**94.44%**
Change	**90**	**780**	**$10,324.17**	**$2.22**	**765**

Utilization Details of Makena® & Hydroxyprogesterone Caproate: FY 2013 (Medical)

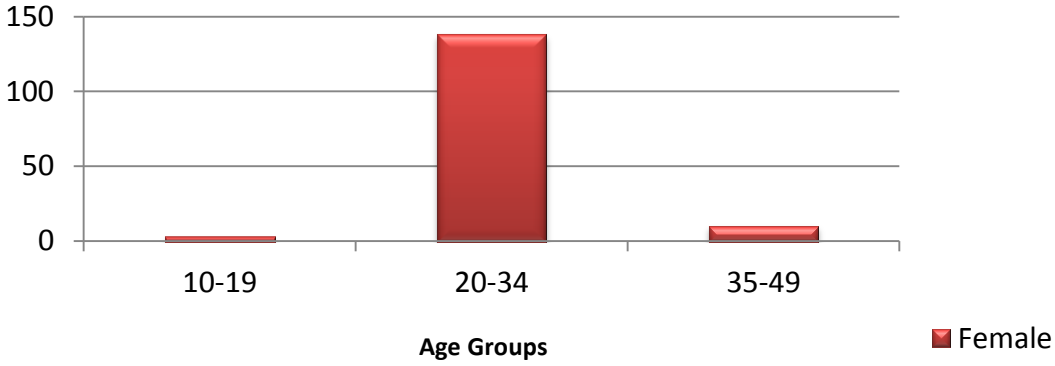
Medication	Claims	Members	Cost	Units	% Cost
Makena® (Brand)	5	2	$2,734.40	1,020	13.66%
17-Hydroxyprogesterone Caproate (Generic)	1,575	250	$17,286.72	1,575	86.34%
Total	**1,580**	**252***	**$20,021.12**	**2,595**	**100.00%**

***Total number of unduplicated members**

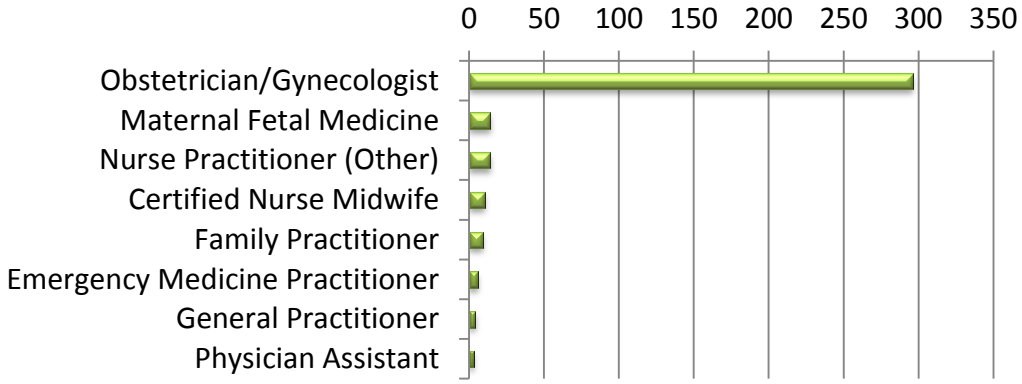
Utilization Details of Makena®: FY 2013 (Pharmacy)

Medication	Claims	Members	Cost	Cost/Day
Makena® (Brand)	**356**	**151**	**$1,287,398.66**	**$120.81**

Demographics of Members Utilizing Makena®: FY 2013



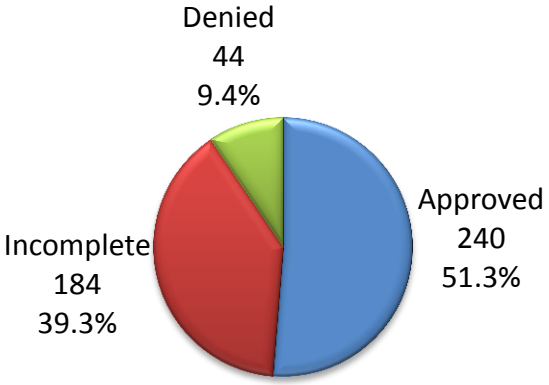
Top Prescriber Specialties of Makena® by Number of Claims: FY 2013



Prior Authorization of Makena®

There were a total of 468 petitions submitted for this medication during fiscal year 2013. The following chart shows the status of the submitted petitions.

Status of Petitions for Makena®: FY 2013



Market News and Update[1,2]

- Anticipated exclusivity expiration of Makena®: 2/2018
- A labeling revision was recently approved by the FDA on 9/16/2013 to include the following changes to the prescribing information:
    - To bold the following Limitation of Use statement listed under the Indications and Use section to increase its prominence: "Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth".
    - To include the additional adverse outcomes under the Postmarketing Experience section:
        - *Pregnancy, puerperium, and perinatal conditions:* cervical incompetence, premature rupture of membranes
        - *Reproductive system and breast disorders:* cervical dilation, shortened cervix
    - To revise the Drug Interactions and Clinical Pharmacology sections to include results of an in vitro study showing the effect of Makena® in inducing or altering the metabolic activities of CYP1A2, 2A6, and 2B6
- The FDA released a statement in June 2012 regarding the compounding of hydroxyprogesterone caproate when a commercially available product (Makena®) is available in which the FDA emphasized that it is applying similar enforcement policies for compounded drugs to compounded hydroxyprogesterone caproate. The compounding of any drug should not exceed the scope of traditional pharmacy compounding, and the FDA generally prioritizes enforcement actions related to compounded drugs using a risk-based approach, giving the highest priority to pharmacies that compound products that are causing harm or that amount to health fraud.

Conclusion and Recommendations

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

---

[1] Drugs @ FDA: Label and Approval History: Makena®. Available online at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Last updated: 9/23/13; Last accessed 9/24/13.

[2] FDA News & Events: Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena®), 6/15/12. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm. Last accessed 9/24/13.

Appendix E

Fiscal Year 2013 Annual Review of Cinryze® and Berinert® (C1 Esterase Inhibitors), Kalbitor® (Ecallentide), and Firazyr® (Icatibant)

Oklahoma Health Care Authority
October 2013

Current Prior Authorization Criteria

The prior authorization of these products was implemented July of 2012. The following are the approval criteria.

Cinryze® (C1 esterase inhibitor) criteria for approval:

1. Documented diagnosis of hereditary angioedema (HAE).
2. For *prophylaxis* of hereditary angioedema.
3. History of at least one or more abdominal or respiratory HAE attacks per month, or history of laryngeal attacks, or three or more emergency medical treatments per year.
4. Documented intolerance, insufficient response, or contraindication to:
    a. Attenuated androgens (e.g. danazol, stanozolol, oxandrolone, methyltestosterone), and
    b. Antifibrinolytic agents (e.g. ε – aminocaproic acid, tranexamic acid), or
    c. Recent hospitalization for severe episode of angioedema.
5. Not currently taking an angiotensin converting enzyme (ACE) inhibitor or estrogen replacement therapy.
6. Dosing:
    a. The recommended dose of Cinryze® is 1,000 units IV every 3 to 4 days, approximately 2 times per week, to be infused at a rate of 1 ml/min.
    b. Initial doses to be administered in outpatient setting by healthcare provider. Patients can be taught by their healthcare provider to self-administer Cinryze® intravenously.
    c. Quantity limit of 8,000 units per month will apply (i.e. 2 treatments per week) or 8 treatments per month.

Berinert® (C1 esterase inhibitor), Kalbitor® (ecallentide), and Firazyr® (icatibant) criteria for approval:

1. Documented diagnosis of hereditary angioedema.
2. For *treatment* of acute attacks of hereditary angioedema.

Utilization of Cinryze®, Berinert®, Kalbitor®, and Firazyr®

Fiscal Year Comparison

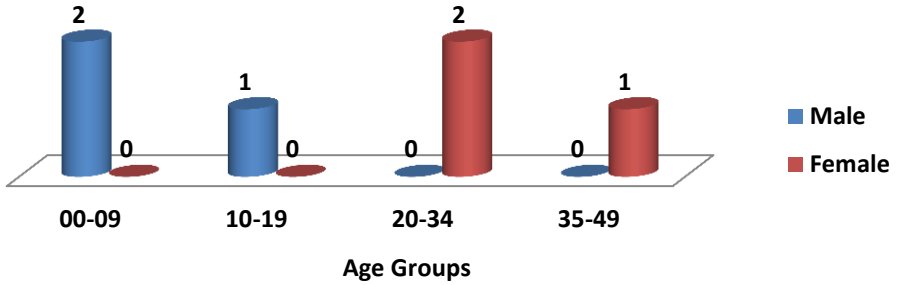
Fiscal Year	Members	Claims	Cost	Cost/Claim	Cost/Day	Units	Days
2012	9	59	$2,300,228.41	$38,986.92	$1,545.85	1,030	1,488
2013	6	26	$978,868.87	$37,648.80	$1,527.10	419	641
% Change	**-33.30%**	**-55.90%**	**-57.40%**	**-3.40%**	**-1.20%**	**-59.30%**	**-56.90%**
Change	**-3**	**-33**	**-1,321,359.54**	**-$1,338.12**	**-$18.75**	**-611**	**-847**

Utilization Details

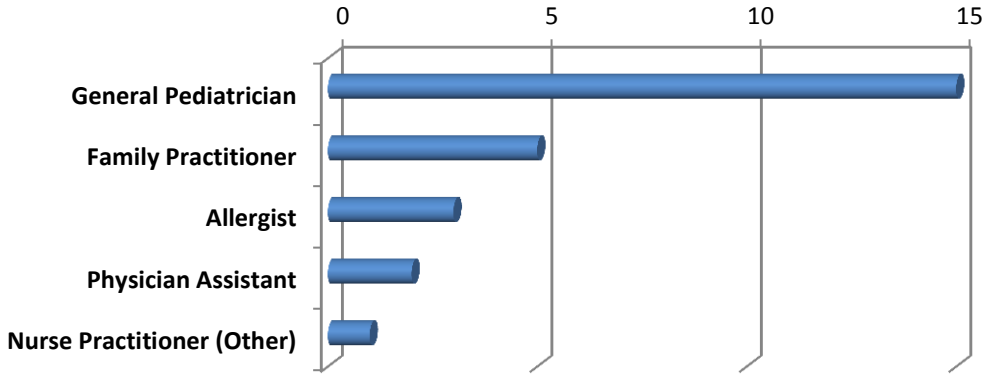
MEDICATION NAME	CLAIMS	UNITS	MEMBERS	DAYS	COST	CLAIMS/ MEMBER	COST/ DAY
CINRYZE SOL 500 UNIT	16	368	3	451	$867,041.85	5.33	$1,922.49
BERINERT INJ 500UNIT	8	33	3	159	$68,744.18	2.67	$432.35
FIRAZYR 30MG/3ML INJ	2	18	2	31	$43,082.84	1	$1,389.77
TOTAL	**26**	**419**	**6***	**641**	**$978,868.87**	**4.33**	**$1,527.10**

*Total number of unduplicated members.

Demographics of Members Utilizing Cinryze®, Berinert®, Kalbitor®, and Firazyr®

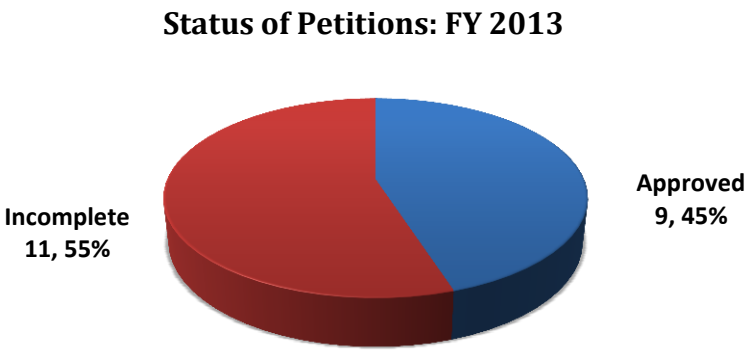


Prescribers of Cinryze®, Berinert®, Kalbitor®, and Firazyr® by Number of Claims



Prior Authorization Status of Cinryze®, Berinert®, Kalbitor®, and Firazyr®: FY 13

There were a total of 20 petitions submitted for Cinryze®, Berinert®, Kalbitor®, and Firazyr® during fiscal year 2013. The following chart shows the status of the submitted petitions:



Market News and Updates

- 01/09/2012- Cinryze® label was revised to include additional safety data including warning and precautions regarding thrombotic events as a result of the Change 3 study. In the open-label trial, there were five serious thrombotic events (n=146) including myocardial infarction, deep vein thrombosis, pulmonary embolism and two events of cerebrovascular accidents. All subjects had underlying risk factors for thrombotic events and it is recommended to monitor patients with known risk factors for thrombotic events closely.[1,2]
- 04/10/2013- Kalbitor® label revision was approved to eliminate the requirement for the Kalbitor® REMS (risk evaluation and mitigation strategy) program.[3]

Conclusions and Recommendations

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

[1] "Vaccines, Blood & Biologics." *January 9, 2012 Approval Letter-CINRYZE*. http://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsblas/fractionatedplasmaproducts/ucm287670.htm.

[2] *HIGHLIGHTS OF PRESCRIBING INFORMATION CINRYZE®*. Web. http://www.cinryze.com/pdfs/cinryze-prescribing-information.pdf.

[3] *Fda.gov*. Web. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/125277Orig1s065ltr.pdf.

Appendix F

Fiscal Year 2013 Annual Review of of Xiaflex®
(Collagenase Clostridium Histolyticum)

Oklahoma Health Care Authority
October 2013

Current Prior Authorization Criteria

The prior authorization of Xiaflex® (collagenase clostridium histolyticum) was implemented in July 2012. The current approval criteria are as follows:

1. FDA approved indication of Dupuytren's contracture with palpable cord, functional impairment and fixed-flexion contractures of the metacarpophalangeal (MP) joint or proximal interphalangeal (PIP) joint of 30 degrees or more.
2. Must be 18 years or older.
3. Not a candidate for needle aponeurotomy.
4. Physician must be trained in treatment of Dupuytren's contracture and injections of the hand.
5. Quantity limit of 3 doses (one dose per 4 weeks) per cord.

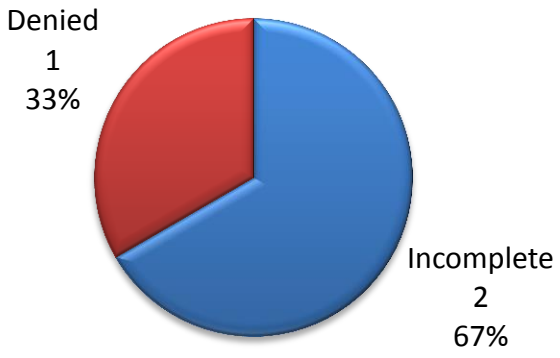
Utilization of Xiaflex®

There has been no use of Xiaflex® during fiscal year 2012 or 2013.

Prior Authorization of Xiaflex®

There were a total of 3 petitions submitted for this product during fiscal year 2013. The following chart shows the status of the submitted petitions.

Status of Petitions for Xiaflex®: FY 2013



Market News and Update

- Anticipated patent expiration of Xiaflex®: 7/2028
- Auxilium Pharmaceuticals, Inc. (manufacturer of Xiaflex®) has filed an application with the FDA to extend the use of Xiaflex® to include the treatment of Peyronie's Disease. The FDA is expected to take action on the application by December 2013.[1]

Conclusion and Recommendations

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

[1] FDA extends PDUFA Goal Date for Auxilium Pharmaceuticals' sBLA for Xiaflex. Medical News. Available online at: http://www.news-medical.net/news/20130828/FDA-extends-PDUFA-goal-date-for-Auxilium-Pharmaceuticals-sBLA-for-XIAFLEX.aspx. Last accessed 10/2/2013.

Appendix G

Fiscal Year 2013 Annual Review of Xgeva® (Denosumab)

Oklahoma Health Care Authority
October 2013

Current Prior Authorization Criteria

The prior authorization of Xgeva® (denosumab) was implemented in March 2012 with the following criteria:

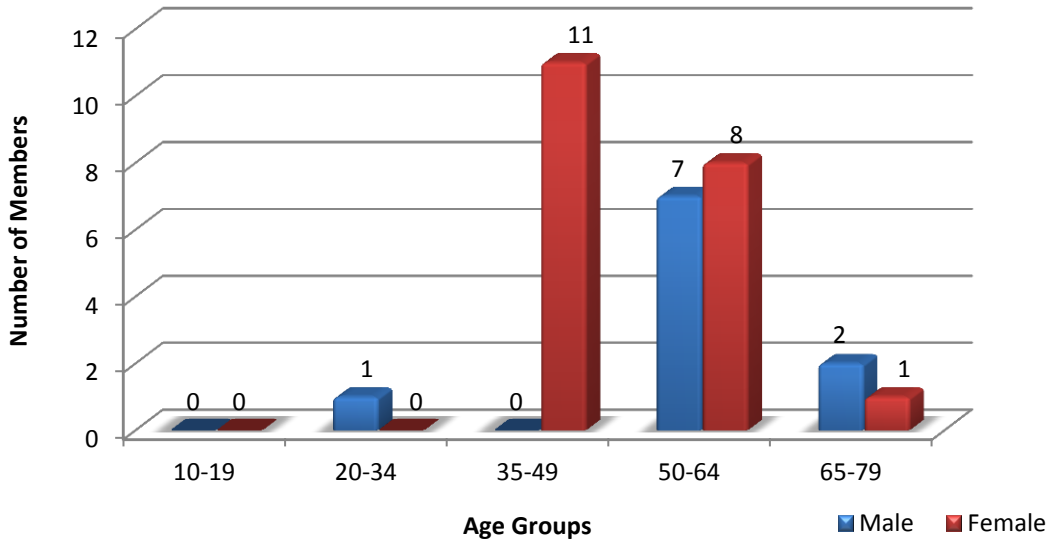
1. FDA approved indication of prevention of skeletal-related events in patients with bone metastases from solid tumors.

Utilization of Xgeva®

Comparison of Fiscal Years Xgeva®: (Medical)

Fiscal Year	Members	Claims	Cost	Cost/Claim	Units
2012	17	49	$78,199.13	$1,595.90	5,227
2013	30	117	$191,775.88	$1,639.11	14,054
% Change	**76.47%**	**138.78%**	**145.24%**	**2.71%**	**168.87%**
Change	**13**	**68**	**$113,576.75**	**$43.21**	**8,827**

Demographics of Members Utilizing Xgeva®: FY 2013



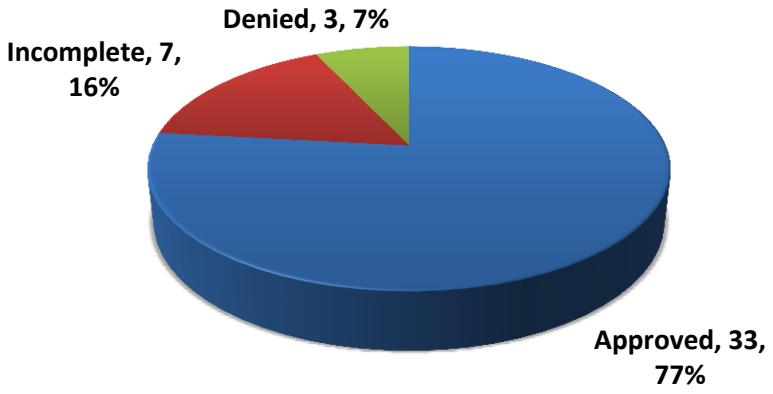
Prescribers of Xgeva® by Number of Claims: FY 2013

Specialty	Number of Claims
Oncologist	116
Urologist	1

Prior Authorization of Xgeva®

There were a total of 43 petitions submitted for this medication during fiscal year 2013. The following chart shows the status of the submitted petitions.

Status of Petitions for Xgeva®: FY 2013



Market News and Update

06/13/13- The FDA expanded the approved use of Xgeva® to treat adults and skeletally mature adolescents with giant cell tumor of the bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity. [1] GCTB is a rare and usually non-cancerous tumor that destroys normal bone as it grows. The new indication has been added to the coverage criteria.

Conclusion and Recommendations

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

[1] Yao, S. (2013, June 13). *FDA approves Xgeva to treat giant cell tumor of the bone*. Retrieved September 17, 2013, from U.S. Food and Drug Administration: www.fda.gov/newsevents/newsroom/pressannouncements/ucm356528.htm

Appendix H

FDA & DEA Updates (additional information can be found at http://www.fda.gov/Drugs/default.htm)

FDA NEWS RELEASE

For Immediate Release: Sept. 10, 2013

FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics

New boxed warning to include neonatal opioid withdrawal syndrome

The U.S. Food and Drug Administration today announced class-wide safety labeling changes and new postmarket study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain.

Given the serious risks of using ER/LA opioids, the class-wide labeling changes, when final, will include important new language to help health care professionals tailor their prescribing decisions based on a patient's individual needs.

The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The updated indication further clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief.

Recognizing that more information is needed to assess the serious risks associated with long-term use of ER/LA opioids, the FDA is requiring the drug companies that make these products to conduct further studies and clinical trials. The goals of these postmarket requirements are to further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death.

The FDA is also requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management according to protocols developed by neonatology experts. NOWS can occur in a newborn exposed to opioid drugs while in the mother's womb. Symptoms may include poor feeding, rapid breathing, trembling, and excessive or high-pitched crying.

In addition, the FDA is notifying ER/LA opioid analgesic application holders of the need for changes to the following sections of drug labeling: Dosage and Administration; Warnings and Precautions; Drug Interactions; Use in Specific Populations; Patient Counseling Information, and the Medication Guide.

Once the safety labeling changes are finalized, modifications will also be made to the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), to reflect the updated information. Originally approved in 2012, the ER/LA Opioid Analgesics REMS requires companies to make available to health care professionals educational programs on how to safely prescribe ER/LA opioid analgesics and to provide Medication Guides and patient counseling documents containing information on the safe use, storage, and disposal of ER/ LA opioids.

FDA NEWS RELEASE

For Immediate Release: Sept. 16, 2013

FDA approves first generic capecitabine to treat colorectal and breast cancers

The U.S. Food and Drug Administration today approved the first generic version of Xeloda (capecitabine), an oral chemotherapy pill used to treat cancer of the colon or rectum (colorectal cancer) that has spread to other parts of the body (metastatic), and metastatic breast cancer.

Teva Pharmaceuticals USA has gained FDA approval to market generic capecitabine in 150 and 500 milligram strengths.

According to the National Cancer Institute, it is estimated that 1.6 million people in the United States will be diagnosed with and 580,000 will die of cancer in 2013. It is estimated that 142,820 people will be diagnosed with and 50,830 will die of cancer of the colon and rectum in 2013. An estimated 232,340 women will be diagnosed with and 39,620 women will die of cancer of the breast in 2013.

In the clinical trials for Xeloda, the most commonly observed adverse reactions included: diarrhea; vomiting; nausea; pain, redness, swelling, or sores in the mouth; hand-and-foot syndrome (pain, swelling, or redness of hands or feet that prevents normal activity); and fever or infection.

It is important that the prescriber know if the patient is also taking a medicine used to thin the blood, such as warfarin. Capecitabine could increase the effect of this medicine, possibly leading to serious side effects. Capecitabine has a boxed warning to alert health care professionals and patients about this risk.

Generic drugs approved by the FDA have the same high quality and strength as brand-name drugs. Generic drug manufacturing and packaging sites must pass the same quality standards as those of brand-name drugs. Information about the availability of generic capecitabine can be obtained from Teva.

FDA NEWS RELEASE

For Immediate Release: Sept. 16, 2013

FDA prohibits manufacture of FDA-regulated drugs from Ranbaxy's Mohali, India, plant and issues import alert

Agency issues import alert and adds this facility to existing consent decree

The U.S. Food and Drug Administration today issued an import alert under which U.S. officials may detain at the U.S. border drug products manufactured at Ranbaxy Laboratories, Ltd.'s facility in Mohali, India. The firm will remain on the import alert until the company complies with U.S. drug manufacturing requirements, known as current good manufacturing practices (CGMP).

"The FDA is committed to using the full extent of its enforcement authority to ensure that drugs made for the U.S. market meet federally mandated quality standards," said Howard Sklamberg, director of the Office of Compliance in the FDA's Center for Drug Evaluation and Research. "We want American consumers to be confident that the drugs they are taking are of the highest quality, and the FDA will continue to work to prevent potentially unsafe products from entering the country."

The FDA also ordered that the Mohali facility be subject to certain terms of the consent decree of permanent injunction entered against Ranbaxy in January 2012. The decree contains provisions to ensure CGMP compliance at certain Ranbaxy facilities, including in Paonta Sahib and Dewas, India, as well as provisions addressing data integrity issues at those two facilities. Ranbaxy's Paonta Sahib and Dewas facilities have been on FDA import alert since 2008.

The FDA exercised its authority under a provision in the consent decree permitting it to order that terms of the decree be extended to a Ranbaxy-owned or operated facility if an inspection determines that the facility is in violation of Federal Food, Drug, and Cosmetic Act or FDA regulations, including CGMP. CGMP requirements serve as the primary regulatory safeguard over drug manufacturing and must be followed by companies to ensure manufacturing quality.

In September and December 2012, FDA inspections identified significant CGMP violations at Ranbaxy's Mohali facility, including failure to adequately investigate manufacturing problems and failure to establish adequate procedures to ensure manufacturing quality.
Under the decree, Ranbaxy is prohibited from manufacturing FDA-regulated drugs at the Mohali facility and introducing drugs into interstate commerce, including into the United States, from the Mohali facility until the firm's methods, facilities, and controls used to manufacture drugs at the Mohali facility are established, operated, and administered in compliance with CGMP. Ranbaxy is required to hire a third-party expert to conduct a thorough inspection of the Mohali facility and certify to the FDA that the facilities, methods, processes, and controls are adequate to ensure continuous compliance with CGMP. Once the agency is satisfied that Ranbaxy has come into compliance with CGMP, Ranbaxy will be permitted to resume manufacturing and distribution of FDA-regulated drugs at the Mohali facility.
The agency does not anticipate that this action will cause a supply disruption or shortage of drugs in the United States.
The FDA recommends that patients not disrupt their drug therapy because this could jeopardize their health. Individuals who are concerned about their medications should talk with their health care professional.

FDA NEWS RELEASE

For Immediate Release: Sept. 30, 2013
FDA approves Perjeta for neoadjuvant breast cancer treatment

First drug approved for use in preoperative breast cancer
The U.S. Food and Drug Administration today granted accelerated approval to Perjeta (pertuzumab) as part of a complete treatment regimen for patients with early stage breast cancer before surgery (neoadjuvant setting). Perjeta is the first FDA-approved drug for the neoadjuvant treatment of breast cancer.
Perjeta was approved in 2012 for the treatment of patients with advanced or late-stage (metastatic) HER2-positive breast cancer. HER2-positive breast cancers have increased amounts of the HER2 protein that contributes to cancer cell growth and survival.
Perjeta's new use is intended for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer (tumor greater than 2 cm in diameter or with positive lymph nodes) who are at high risk of having their cancer return or spread (metastasize) or of dying from the disease. It is to be used in combination with trastuzumab and other chemotherapy prior to surgery and, depending upon the treatment regimen used, may be followed by chemotherapy after surgery. Following surgery, patients should continue to receive trastuzumab to complete one year of treatment.
In May 2012, the FDA issued a draft guidance about the use of pathologic complete response (pCR), defined as the absence of invasive cancer in the breast and lymph nodes, as an endpoint to support accelerated approval of a drug for neoadjuvant treatment of high-risk, early stage breast cancer. Under the FDA's accelerated approval program, patients are provided access to promising drugs to treat serious or life-threatening conditions while confirmatory clinical trials are conducted.
Perjeta's accelerated approval for neoadjuvant treatment is based on a study designed to measure pCR. In the study, 417 participants were randomly assigned to receive one of four neoadjuvant treatment regimens: trastuzumab plus docetaxel, Perjeta plus trastuzumab and docetaxel, Perjeta plus trastuzumab or Perjeta plus docetaxel. About 39 percent of participants who received Perjeta plus trastuzumab and docetaxel achieved pCR, compared to about 21 percent who received trastuzumab plus docetaxel.
The confirmatory trial for this accelerated approval is being conducted in participants with HER2-positive breast cancer who had prior breast cancer surgery and are at high risk of having their cancer return. More than 4,800 participants are enrolled in this trial, which will provide further data on efficacy, safety and long-term outcomes. Results are expected in 2016.
The most common side effects reported in participants receiving Perjeta plus trastuzumab and docetaxel were hair loss, diarrhea, nausea and a decrease in infection-fighting white blood cells. Other significant side effects included decreased cardiac function, infusion-related reactions, hypersensitivity reactions and anaphylaxis.

The FDA reviewed Perjeta's use for neoadjuvant treatment under the agency's priority review program, which provides for an expedited review of drugs that may offer major advances in treatment.
Breast cancer is the second leading cause of cancer-related death among women. An estimated 232,340 women will be diagnosed with breast cancer, and 39,620 will die from the disease in 2013, according to the National Cancer Institute. Almost 20 percent of breast cancers have increased amounts of the HER2 protein.
Perjeta is marketed by Genentech, a member of the Roche Group, based in South San Francisco, Calif.

Safety Announcements

FDA Drug Safety Communication: FDA requiring color changes to Duragesic (fentanyl) pain patches to aid safety—emphasizing that accidental exposure to used patches can cause death

Safety Announcement
[9-23-2013] The U.S. Food and Drug Administration (FDA) is requiring color changes to the writing on Duragesic (fentanyl) pain patches so they can be seen more easily. This is part of an effort to prevent accidental exposure to the patches, which can cause serious harm and death in children, pets, and others. Similar changes are being requested for the generic fentanyl patches. We are also reminding patients and health care professionals that fentanyl patches are dangerous even after they've been used because they still contain high amounts of strong narcotic pain medicine. Used fentanyl patches require proper disposal after use—fold the patch, sticky sides together, and flush it down the toilet right away.
Patients should be aware that patches that are not stuck to the skin tightly enough may accidentally fall off a patient and stick to someone in close contact, such as a child. To prevent this, patients should check periodically, by sight or touch, to make sure the patch is still sticking to the skin properly. Patients should tape down the edges of a patch that become loose or cover the patch with a sticky adhesive film such as Bioclusive or Tegaderm.
We continue to learn of deaths from accidental exposure to fentanyl patches, including two additional deaths in children since our last warning to the public in April 2012 about this safety concern.
As part of our ongoing effort to minimize the risk of accidental exposure to fentanyl patches, we are requiring the manufacturer of Duragesic to print the name and strength of the drug on the patch in long-lasting ink, in a color that is clearly visible to patients and caregivers. The current ink color varies by strength and is not always easy to see. This change is intended to enable patients and caregivers to more easily find patches on patients' bodies and see patches that have fallen off, which children or pets could accidentally touch or ingest. The manufacturers of generic fentanyl patches are being requested to make similar changes.
In addition, our "Safe Use Initiative" is working to create awareness and educational opportunities for health care professionals, patients, and caregivers about the safe storage and proper disposal of fentanyl patches.
We urge patients to read the "Medication Guide and Instructions for Use" that comes with their fentanyl patch prescriptions. In addition to informing patients about the correct use of fentanyl patches, health care professionals should also explain to patients and caregivers the appropriate storage and disposal each time they write a prescription for these patches. Anyone accidentally exposed to a fentanyl patch should immediately seek emergency medical attention or call the toll-free Poison Help Line at 1-800-222-1222.

Safety Announcements

FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning

Safety Announcement
[9-27-2013] The U.S. Food and Drug Administration (FDA) is warning that an additional analysis shows an increased risk of death when intravenous (IV) Tygacil (tigecycline) is used for FDA-approved uses as well as for non-approved uses. As a result, we approved a new *Boxed Warning* about this risk to be added to the Tygacil drug label and updated the *Warnings and Precautions* and the *Adverse Reactions* sections. A *Boxed Warning* is the strongest warning given to a drug. These changes to the Tygacil label are based on an additional

analysis that was conducted for FDA-approved uses after issuing a Drug Safety Communication (DSC) about this safety concern in September 2010.
Health care professionals should reserve Tygacil for use in situations when alternative treatments are not suitable. Tygacil is FDA-approved to treat complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CABP). Tygacil is not indicated for treatment of diabetic foot infection or for hospital-acquired or ventilator-associated pneumonia.
Patients and their caregivers should talk with their health care professionals if they have any questions or concerns about Tygacil.
In the 2010 DSC, we informed the public that a combined analysis, or meta-analysis, of 13 Phase 3 and 4 trials showed a higher risk of death among patients receiving Tygacil compared to other antibacterial drugs: 4.0% (150/3788) vs. 3.0% (110/3646) respectively. The adjusted risk difference for death was 0.6% with corresponding 95% confidence interval (0.1, 1.2). The increased risk was greatest in patients treated with Tygacil for ventilator-associated pneumonia, a use for which FDA has not approved the drug.
Since issuing the 2010 DSC, we analyzed data from 10 clinical trials conducted only for FDA-approved uses (cSSSI, cIAI, CABP), including trials conducted after the drug was approved. This analysis showed a higher risk of death among patients receiving Tygacil compared to other antibacterial drugs: 2.5% (66/2640) vs. 1.8% (48/2628), respectively. The adjusted risk difference for death was 0.6% with corresponding 95% confidence interval (0.0%, 1.2%). In general, the deaths resulted from worsening infections, complications of infection, or other underlying medical conditions.

Current Drug Shortages Index (as of September 30, 2013):

The information provided in this section is provided voluntarily by manufacturers.

Acetylcysteine Inhalation Solution UPDATED 9/24/2013
Acyclovir Sodium Injection (initial posting 11/13/2012)
Alteplase (Cathflo Activase) (initial posting 1/27/2012)
Amikacin Injection
Aminocaproic Acid Injection (initial posting 3/8/2013) UPDATED 9/24/2013
Aminophylline (initial posting 12/10/2012) UPDATED 9/24/2013
Ammonium Chloride Injection (initial posting 3/8/2013)
Amytal Sodium Injection (initial posting date 1/31/2013)
Atracurium Besylate (initial posting 2/27/2012)
Atropine Sulfate Injection UPDATED 9/24/2013
Barium Sulfate for Suspension (initial posting 10/12/2012)
Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride (Helidac) (initial posting 3/8/2012)
Bumetanide Injection (initial posting 6/21/2012) UPDATED 9/24/2013
Bupivacaine Hydrochloride (Marcaine, Sensorcaine) Injection UPDATED 9/24/2013
Buprenorphine Hydrochloride (Buprenex) Injection
Caffeine and Ergotamine Tartrate (Cafergot) Tablets (initial posting 3/8/2012)
Caffeine Anhydrous (125mg/mL); Sodium Benzoate (125mg/mL) Injection
Calcium Chloride Injection (initial posting 12/13/2012) UPDATED 9/26/2013
Calcium Gluconate Injection (initial posting 1/10/2013) UPDATED 9/26/2013
Chromic Chloride Injection UPDATED 9/24/2013
Cidofovir Injection (initial posting 2/15/2013)
Citric Acid; Gluconolactone; Magnesium Carbonate (Renacidin) Solution for Irrigation (initial posting 6/30/2012)
Copper (Cupric Chloride) Injection (initial posting 4/25/2013)
Cyanocobalamin Injection (initial posting 1/25/2013) UPDATED 9/26/2013
Daunorubicin Hydrochloride Solution for Injection
Denileukin Diftitox (Ontak) (initial posting 9/22/2012)
Desmopressin Acetate (DDAVP) Injection (initial posting 5/7/2013)

Dexamethasone Sodium Phosphate Injection (initial posting 1/15/2013)
Dexrazoxane (Zinecard) Injection
Dextrose Injection (initial posting 5/23/2012) UPDATED 9/24/2013
Dipyridamole Injection (initial posting 7/24/2012)
Dobutamine Hydrochloride Injection (initial posting 4/26/2013) UPDATED 9/24/2013
Doxorubicin (Adriamycin) Lyophilized Powder (initial posting 12/2/2011)
Doxycycline Hyclate (initial posting 1/18/2013)
Epinephrine Injection (initial posting 4/27/2012) UPDATED 9/26/2013
Epinephrine 1mg/mL (Preservative Free) (initial posting 6/21/2012)
Ethiodol (Ethiodized Oil) Ampules
Etomidate (Amidate) Injection (initial posting 2/9/2012)
Fentanyl Citrate (Sublimaze) Injection UPDATED 9/24/2013
Fluphenazine Decanoate Injection 4/25/2013
Fluphenazine Hydrochloride Injection
Fluticasone Propionate and Salmeterol (Advair HFA) Inhalation Aerosol (initial posting date) - 10/17/2012)
Fosphenytoin Sodium (Cerebyx) Injection (initial posting 3/30/2012)
Furosemide Injection (initial posting 6/20/2012)
Gallium Nitrate (Ganite) Injection (initial posting 4/4/2012)
Heparin Sodium Injection (initial posting 7/5/2012) UPDATED 9/24/2013
Hydromorphone Hydrochloride (Dilaudid) Injection (initial posting 3/7/2012) UPDATED 9/24/2013
Hydromorphone Hydrochloride Tablets (initial posting 2/19/2013)
Ibandronate Sodium (Boniva) Injection (initial posting 6/6/2012)
Intravenous Fat Emulsion
Isoniazid; Rifampin (Rifamate) Capsules 3/15/2013 UPDATED 9/25/2013
Ketorolac Tromethamine Injection UPDATED 9/24/2013
Leucovorin Calcium Lyophilized Powder for Injection
Leuprolide Acetate Injection
Levothyroxine Sodium (Levoxyl) Tablets (initial posting date - 3/15/2013)
Lidocaine Hydrochloride (Xylocaine) Injection (initial posting date - 2/22/2012) UPDATED 9/24/2013
Liotrix (Thyrolar) Tablets
Lomustine Capsules (initial posting date - 5/9/2013)
Lorazepam (Ativan) Injection
Magnesium Sulfate Injection UPDATED 9/24/2013
Mannitol (Osmitrol, Resectisol) Injection (initial posting date - 12/21/2011) UPDATED 9/24/2013
Mecasermin [rDNA origin] (Increlex) Injection (initial posting date - 4/26/2013)
Methazolamide (Glauctabs, Neptazane) Tablets
Methyldopate Hydrochloride Injection
Methylin Chewable Tablets (initial posting date - 2 /19/2013)
Methylphenidate Hydrochloride ER Tablets (initial posting date - 2/19/2013)
Methylphenidate Hydrochloride Tablets (initial posting date - 2/19/2013) UPDATED 9/26/2013
Metoclopramide (Reglan) Injection
Morphine Sulfate Injection UPDATED 9/24/2013
Morphine Sulfate (Astramorph PF, Duramorph, Infumorph) Injection (Preservative Free) UPDATED 9/24/2013
Multi-Vitamin Infusion (Adult and Pediatric)
Nalbuphine Hydrochloride (Nubain) Injection (initial posting 5/15/2012) UPDATED 9/24/2013
Neostigmine Methylsulfate Injection (initial posting 1/14/2013)
Nitroglycerin Ointment USP, 2% (Nitro-Bid) (Initial posting 10/23/2012) UPDATED 9/25/2013
Ondansetron (Zofran) 2mg/mL Injection UPDATED 9/24/2013
Oseltamivir Phosphate (Tamiflu) Powder for Oral Suspension (Initial posting 1/10/2013)
Pancuronium Bromide Injection
Papaverine Hydrochloride Injection (initial posting 12/17/2012)

Pentamidine Isethionate (NebuPent) Inhalant (initial posting 8/27/2012)
Pentamidine Isethionate (Pentam 300) Injection (initial posting 8/27/2012)
Phosphate (Glycophos) Injection (initial posting 5/29/2013)
Pilocarpine HCL Opthalmic Gel 4% (Pilopine HS) (initial posting 6/1/2012)
Potassium Acetate Injection, USP 2mEq/mL
Potassium Chloride Injection (initial posting 5/15/2012) UPDATED 9/24/2013
Potassium Phosphate Injection
Procainamide HCL Injection
Prochlorperazine Injection (initial posting 1/30/2012)
Promethazine Injection (initial posting 2/10/2012)
Reserpine Tablets (initial posting 4/17/2013)
Rifampin for Injection (initial posting 3/22/2013)
Secretin Synthetic Human (ChiRhoStim) Injection (ChiRhoStim) (initial posting 6/15/2012)
Selenium Injection
Sincalide (Kinevac) Lyophilized Powder for Injection (initial posting 6/21/2013)
Sodium Acetate Injection (initial posting 1/31/2012)
Sodium Chloride 0.9% (5.8mL and 20mL) (initial posting 5/4/2012)
Sodium Chloride 23.4%
Sodium Phosphate Injection
Succinylcholine (Anectine, Quelicin) Injection (initial posting 8/17/2012)
Sufentanil Citrate (Sufenta) Injection UPDATED 9/24/2013
Sulfamethoxazole 80mg/ml;Trimethoprim 16mg/ml (SMX/TMP) (Bactrim) Injection
Technetium TC-99M Albumin Aggregated Kit (initial posting 9/3/2013) UPDATED 9/17/2013
Technetium Tc99m Bicisate for Injection (Neurolite) (initial posting 5/4/2012)
Technetium Tc99m Sestamibi Kit for Injection (Cardiolite) (initial posting 5/4/2012)
Telavancin (Vibativ) Injection
Tetracycline Capsules
Thiotepa (Thioplex) for Injection
Ticarcillin Disodium/Clavulanic Potassium (Timentin) Injection (initial posting 8/16/12)
Tobramycin Solution for Injection
Trace Elements (initial posting 1/24/2013)
Tromethamine (Tham) Injection (initial posting 5/2/2012)
Verapamil Hydrochloride Injection, USP (initial posting 4/17/2013) UPDATED 9/24/2013
Vinblastine Sulfate Injection (initial posting 1/31/2012)
Vitamin A Palmitate (Aquasol A)
Zinc Injection (initial posting 2/15/2012)