Appendix G

Fiscal Year 2010 Annual Review of Antihypertensives and 30 Day Notice to Prior Authorize Tribenzor® (olmesartan medoxomil / amlodipine besylate / HCTZ), Tekamlo® (aliskiren hemifumarate/amlodipine besylate), Nexiclon XR® (clonidine extended-release), and Catapres-TTS® (clonidine transdermal patch)

Oklahoma HealthCare Authority
January 2011

Current Prior Authorization Criteria

There are 7 categories of antihypertensive medications currently included in the Product Based Prior Authorization program:

1. Calcium Channel Blockers (**CCBs**)
2. Angiotensin I Converting Enzyme Inhibitors (**ACEIs**)
3. **ACE/CCBs** Combination Products
4. ACE inhibitor and hydrochlorathiazide combination products (**ACEI/HCTZs**)
5. Angiotensin II Receptor Blockers (**ARBs**)
6. ARB combination products (**ARB Combinations**)
7. Direct Renin Inhibitors (**DRIs**) and DRI Combination products

To qualify for a Tier 2 antihypertensive medication (or Tier 3 medication when no Tier 2 medications exist) there must be

1. documented inadequate response to two Tier 1 medications, or
2. adverse drug reaction to all Tier 1 class of medications, or
3. previous stabilization on the Tier 2 medication, or
4. a unique indication for which the Tier 1 antihypertensives lack

To qualify for a Tier 3 antihypertensive medication there must be

1. documented inadequate response to two Tier 1 medications and documented inadequate response to all available Tier 2 medications, or
2. adverse drug reaction to all Tier 1 or Tier 2 classes of medications, or
3. previous stabilization on the Tier 3 medication, or
4. a unique indication for which the lower tiered antihypertensives lack

Criteria for DRIs Authorization

1. FDA approved indication.
2. Recent trial, within the previous 6 months and at least 4 weeks in duration, of an ACE Inhibitor (or an ARB if previous trial of an ACEI) and a diuretic, used concomitantly at recommended doses, that did not yield adequate blood pressure control.
3. May be used in either monotherapy or combination therapy.

Calcium Channel Blockers (CCB medications)		
Tier-1	**Tier-2**	**Tier-3**
amlodipine (Norvasc®)	diltiazem (Cardizem® LA)	
diltiazem (Cardizem®)	nicardipine (Cardene® SR)	
diltiazem (Tiazac®, Taztia XT®)	verapamil (Covera-HS®)	
diltiazem CD (Cardizem® CD)	nisoldipine (Sular®)	
diltiazem ER (Cartia XT®, Diltia XT®)	amlodipine/atorvastatin (Caduet®)	
diltiazem SR (Cardizem® SR)		
diltiazem XR (Dilacor® XR)		
felodipine (Plendil®)		
isradipine (Dynacirc®, Dynacirc CR®)		
nicardipine (Cardene®)		
nifedipine (Adalat®, Procardia®)		
nifedipine CC (Adalat® CC)		
nifedipine ER		
nifedipine XL (Nifedical XL®, Procardia XL®)		
nimodipine (Nimotop®)		
verapamil (Calan®, Isoptin®, Verelan®)		
verapamil SR		

ARBs (Angiotensin Receptor Blockers) and ARB Combination Products		
Tier-1	**Tier-2**	**Tier-3**
Any Tier-1 ACE Inhibitor:	amlodopine / valsartan (Exforge®)	amlodipine / olmesartan (Azor™)
benazepril (Lotensin®)	amlodopine / valsartan (Exforge® HCT)	candesartan (Atacand®)
captopril (Capoten®)	irbesartan (Avapro®)	candesartan / HCTZ (Atacand® HCT)
enalapril (Vasotec®)	irbesartan / HCTZ (Avalide®)	losartan (Cozaar®)
enalaprilat (Vasotec® IV)	valsartan (Diovan®)	losartan / HCTZ (Hyzaar®)
fosinopril (Monopril®)	valsartan / HCTZ (Diovan HCT®)	eprosartan (Teveten®)
lisinopril (Prinivil®, Zestril®)	olmesartan (Benicar®)	eprosartan / HCTZ (Teveten® HCT)
moexipril (Univasc®)	olmesartan / HCTZ (Benicar HCT®)	telmisartan/amlodipine (Twynsta)
quinapril (Accupril®)	telmisartan (Micardis®)	
trandolapril (Mavik®)	telmisartan / HCTZ (Micardis® HCT)	
ramipril (Altace®)		

Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)		
Tier-1	**Tier-2**	**Tier-3**
benazepril (Lotensin®)		perindopril erbumine (Aceon®)
captopril (Capoten®)		
enalapril (Vasotec®)		
enalaprilat (Vasotec® IV)		
fosinopril (Monopril®)		
lisinopril (Prinivil®, Zestril®)		
moexipril (Univasc®)		
quinapril (Accupril®)		
trandolapril (Mavik®)		
ramipril (Altace®)		
ACE Inhibitor / Calcium Channel Blocker Combinations		
Tier-1 ACE + Tier 1 CCB	trandolapril / verapamil (Tarka®)	
	benazepril / amlodipine (Lotrel®)	
	enalapril / felodipine (Lexxel®)	

ACE Inhibitor / HCTZ Combinations		
benazepril/HCTZ (Lotensin® HCT)		
captopril/HCTZ (Capozide®)		
enalapril/HCTZ (Vasoretic®)		
fosinopril/HCTZ (Monopril-HCT®)		
lisinopril/HCTZ (Prinzide®,Zestoretic®)		
moexipril/HCTZ (Uniretic®)		

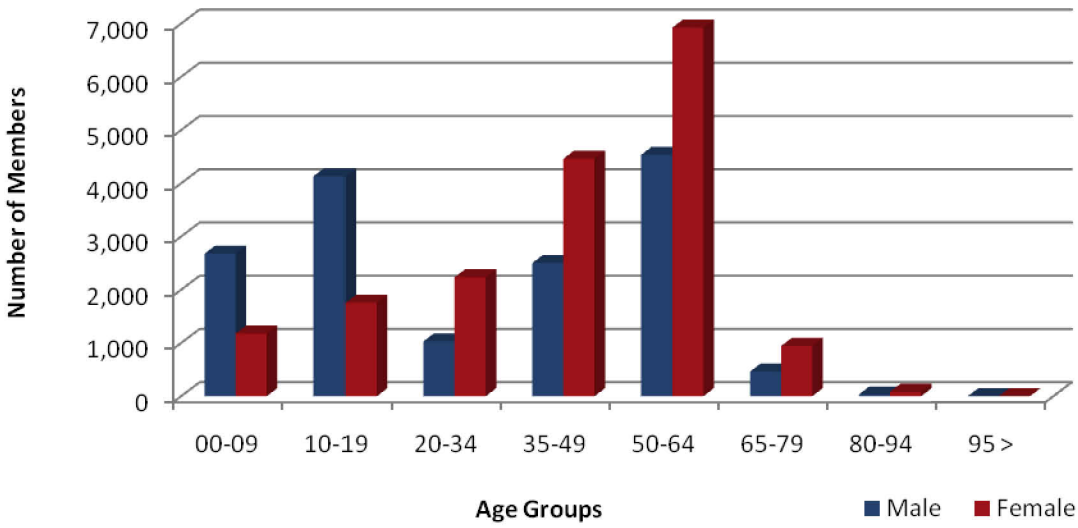
Direct Renin inhibitors		
Tier-1	**Tier-2**	**Tier-3**
Tier-1 ACE Inhibitor + Diuretic	ARB + Diuretic	Aliskiren (Tekturna®)
		Aliskiren/HCTZ (Tekturna HCT®)
		Aliskiren/valsartan (Valturna®)

Utilization of Antihypertensives

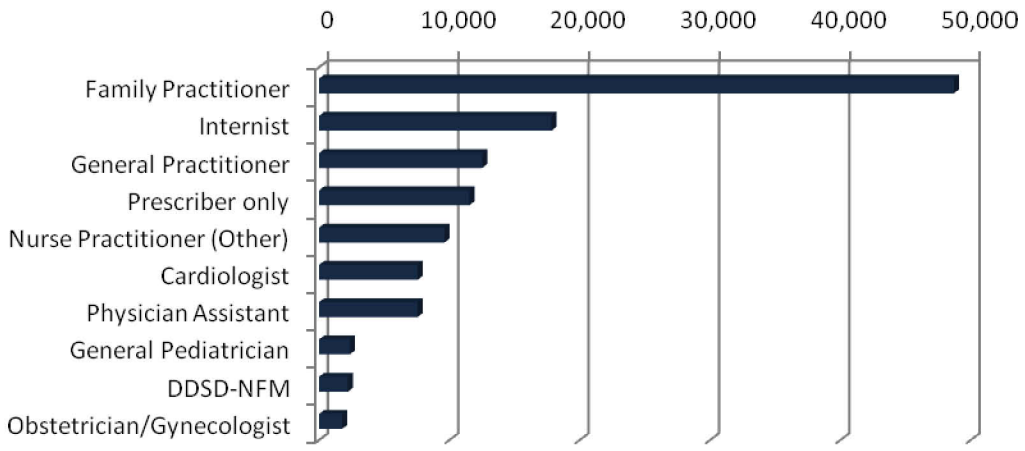
Comparison of Fiscal Years

Fiscal Year	Members	Claims	Cost	Cost/Claim	Perdiem	Units	Days
2009	22,619	118,861	$2,862,873.68	$24.09	$0.63	5,624,885	4,546,064
2010	25,919	129,862	$2,807,841.22	$21.62	$0.56	6,639,819	5,013,106
Percent Change	14.60%	9.30%	-1.9%	-10.30%	-11.10%	18.00%	10.30%
Change	3,300	11,001	-$55,035.46	-$2.47	-$0.07	1,014,934	467,042

Demographics of Members Utilizing Antihypertensives for FY 2010



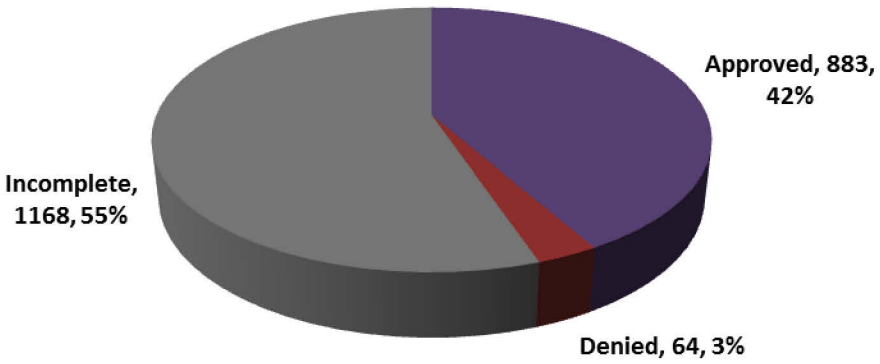
Prescribers of Antihypertensives by Number of Claims for FY 2010



Prior Authorization of Antihypertensives

There were a total of 2,115 petitions submitted for this PBPA category during fiscal year 2010. Please note that for this PBPA category the system will automatically search Tier 1 medications in member's claims history within a certain timeframe and if detected, the member can automatically get the Tier 2 medication without submitting a prior authorization form. The bottom chart shows the details of the petition submitted.

Status of Petitions for Antihypertensives: FY 2010



Market News and Update

- **Tribenzor®** (olmesartan medoxomil / amlodipine besylate / hydrochlorothiazide) was approved in July 2010.
  - Available as 20/5/12.5 mg, 40/5/12.5 mg, 40/5/25 mg, 40/10/12.5 mg, and 40/10/25 mg tablets
  - Cost of therapy is approximately $80-$124 per 30 tablets depending on the dose.

- **Tekamlo®** (aliskiren hemifumarate/amlodipine besylate) was approved in January 2010.
  - Available as 150mg/5mg, 150mg/10mg, 300mg/5mg, 300mg/10mg tablets.
  - Cost of therapy is $79-$99 per 30 tablets depending on the dose.

- **Nexiclon XR®** (clonidine) was approved October 2010.
  - Indicated for the treatment of hypertension.
  - Extended-release formulation of clonidine available as 0.17 mg and 0.26 mg tablets (equivalent to 0.2 mg and 0.3 mg of immediate release clonidine, respectively), and a 0.09 mg/mL oral suspension.
  - Initial dose is 0.17 mg once daily to be administered at bedtime. Dose should be increased in 0.09 mg increments as needed; therapeutic doses range from 0.17 mg to 0.52 mg once daily.
  - Dose should be adjusted for renal impairment.
  - Adverse events are similar to immediate release clonidine. The most common are dry mouth, drowsiness, and dizziness.
  - Based on in vitro studies, high concentration of alcohol may increase the rate of release of Nexiclon XR®.
  - Cost of therapy is $127 per 30 tablets of the 0.17 mg strength. Cost is currently not known for the other doses. Cost of therapy for immediate-release clonidine is 0.10 per tablet for all strengths.

- **Catapres TTS®** (clonidine weekly transdermal patch)
  - Price ranges for generic and brand patches (#4 per 28 days)
    - 0.1 mg: $101-$130
    - 0.2 mg: $171-$219
    - 0.3 mg: $237-$303

- **New generic approvals**:
  - Losartan and losartan /HCTZ were approved April 2010. They are now available as multi-source products and have a State Maximum Allowable Cost designation.
  - Glenmark Pharmaceuticals launched the generic version of Abbott's Tarka® (trandolapril/verapamil) tablets in June 2010, which subsequently had to be removed from the market. Although these products are AB-rated and the FDA has granted approval for the generic version of Tarka, Glenmark and Abbott are in patent litigation. The patent for Tarka® expires on February 24, 2015.

Conclusion and Recommendations

The College of Pharmacy recommends the following changes to the Antihypertensives PBPA category:

1. Move Cozaar (losartan) and Hyzaar (losartan /HCTZ) into Tier 1 of the ARB category.
2. Placement of Tribenzor® (olmesartan/amlodipine/HCTZ) in Tier 3 of the ARB category.
3. Placement of Tekamlo® (Aliskiren/amlodipine) into Tier 3 of the DRI category.
4. Prior Authorization of Nexiclon XR® (clonidine extended release) and Catapres TTS® Patch (clonidine) with the following criteria :
   a. FDA-approved indication of hypertension in adults
   b. Must provide a clinically significant reason why the member cannot take clonidine immediate release tablets.
5. Changes to the antihypertensive prior authorization criteria as follows :

To qualify for a Tier 2 antihypertensive medication (or Tier 3 medication when no Tier 2 medications exist) there must be

1. documented inadequate response to two Tier 1 medications (trials must include medication from all available classes where applicable), or
2. adverse drug reaction to all Tier 1 class of medications, or
3. previous stabilization on the Tier 2 medication, or
4. a unique indication for which the Tier 1 antihypertensives lack

To qualify for a Tier 3 antihypertensive medication there must be

1. documented inadequate response to two Tier 1 medications and documented inadequate response to all available Tier 2 medications, or
2. adverse drug reaction to all Tier 1 or Tier 2 classes of medications, or
3. previous stabilization on the Tier 3 medication, or
4. a unique indication for which the lower tiered antihypertensives lack

ARBs (Angiotensin Receptor Blockers) and ARB Combination Products		
Tier-1	**Tier-2**	**Tier-3**
Any Tier-1 ACE Inhibitor:	amlodopine / valsartan (Exforge®)	candesartan (Atacand®)
benazepril (Lotensin®)	amlodopine / valsartan (Exforge® HCT)	candesartan / HCTZ (Atacand® HCT)
captopril (Capoten®)	amlodipine / olmesartan (Azor™)	eprosartan (Teveten®)
enalapril (Vasotec®)	irbesartan (Avapro®)	eprosartan / HCTZ (Teveten® HCT)
enalaprilat (Vasotec® IV)	irbesartan / HCTZ (Avalide®)	telmisartan/amlodipine (Twynsta)
fosinopril (Monopril®)	valsartan (Diovan®)	telmisartan (Micardis®)
lisinopril (Prinivil®, Zestril®)	valsartan / HCTZ (Diovan HCT®)	telmisartan / HCTZ (Micardis® HCT)
moexipril (Univasc®)	olmesartan (Benicar®)	**olmesarten/amlodipine/HCTZ (Tribenzor®)**
quinapril (Accupril®)	olmesartan / HCTZ (Benicar HCT®)	
trandolapril (Mavik®)		
ramipril (Altace®)		
losartan (Cozaar®)		
losartan / HCTZ (Hyzaar®)		

Direct Renin inhibitors (Tekturna®)		
Tier-1	**Tier-2**	**Tier-3**
Tier-1 ACE Inhibitor + Diuretic	ARB + Diuretic	Aliskiren (Tekturna®)
		Aliskiren/HCTZ (Tekturna HCT®)
		Aliskiren/valsartan (Valturna®)
		Aliskiren/amlodipine (Tekamlo®)

Utilization Details of Antihypertensives for Fiscal Year 2010

BRAND NAME	CLAIMS	UNITS	DAYS	MEMBERS	PAID	UNITS/ DAY	CLAIMS/ CLIENT	PER DIEM	PERCENT PAID
CALCIUM CHANNEL BLOCKERS									
AMLODIPINE TAB 2.5MG	861	33,682	29,742	249	$6,231.21	1.13	3.46	$0.21	0.23%
AMLODIPINE TAB 5MG	7,407	297,470	274,823	2,191	$54,602.06	1.08	3.38	$0.20	2.00%
NORVASC TAB 5MG	6	180	165	1	$369.17	1.09	6	$2.24	0.01%
AMLODIPINE TAB 10MG	9,632	393,809	373,121	2,447	$81,442.08	1.06	3.94	$0.22	2.98%
NORVASC TAB 10MG	22	1,080	1,080	4	$3,002.16	1	5.5	$2.78	0.11%
DILTIAZEM TAB 30MG	174	12,117	5,016	58	$1,610.89	2.42	3	$0.32	0.06%
DILTIAZEM TAB 60MG	349	25,963	10,682	99	$3,387.11	2.43	3.53	$0.32	0.12%
DILTIAZEM TAB 90MG	204	16,480	6,321	49	$2,629.83	2.61	4.16	$0.42	0.10%
DILTIAZEM TAB 120MG	313	17,696	10,456	95	$3,229.45	1.69	3.29	$0.31	0.12%
DILTIAZEM CAP 60MG ER	35	1,900	1,295	13	$977.67	1.47	2.69	$0.75	0.04%
DILTIAZEM CAP 90MG ER	34	2,002	1,102	7	$1,303.99	1.82	4.86	$1.18	0.05%
DILTIAZEM CAP 120MG ER	46	2,350	1,370	15	$2,115.47	1.72	3.07	$1.54	0.08%
DILTIAZEM CAP 120MG ER	194	8,186	6,983	65	$3,887.23	1.17	2.98	$0.56	0.14%
DILT-XR CAP 120MG	116	5,646	4,879	42	$2,404.37	1.16	2.76	$0.49	0.09%
DILTIAZEM CAP 180MG ER	247	10,840	8,956	73	$5,263.16	1.21	3.38	$0.59	0.19%
DILT-XR CAP 180MG	117	6,536	5,470	38	$2,682.45	1.19	3.08	$0.49	0.10%
DILTIAZEM CAP 240MG ER	364	16,524	14,304	111	$9,218.75	1.16	3.28	$0.64	0.34%
DILT-XR CAP 240MG	201	9,636	8,486	64	$5,009.65	1.14	3.14	$0.59	0.18%
DILTIAZEM CAP 120MG/24	97	3,763	3,443	32	$2,297.63	1.09	3.03	$0.67	0.08%
TAZTIA XT CAP 120MG/24	9	335	335	4	$197.01	1	2.25	$0.59	0.01%
DILTZAC CAP 120MG/24	5	330	330	4	$181.65	1	1.25	$0.55	0.01%
DILTIAZEM CAP 180MG/24	76	4,000	2,996	26	$2,792.88	1.34	2.92	$0.93	0.10%
TAZTIA XT CAP 180MG/24	18	900	750	7	$609.32	1.2	2.57	$0.81	0.02%
DILTZAC CAP 180MG/24	9	600	390	3	$393.17	1.54	3	$1.01	0.01%
DILTIAZEM CAP 240MG/24	101	4,490	3,630	26	$4,391.44	1.24	3.88	$1.21	0.16%
DILTZAC CAP 240MG/24	31	1,120	1,120	11	$935.23	1	2.82	$0.84	0.03%
TAZTIA XT CAP 240MG/24	29	1,147	1,147	11	$1,103.04	1	2.64	$0.96	0.04%
DILTIAZEM CAP 300MG/24	32	1,450	1,450	10	$1,684.73	1	3.2	$1.16	0.06%
TAZTIA XT CAP 300MG/24	16	660	660	3	$705.74	1	5.33	$1.07	0.03%
DILTZAC CAP 300MG/24	14	598	598	3	$557.23	1	4.67	$0.93	0.02%
DILTIAZEM CAP 360MG/24	150	7,100	7,040	42	$8,506.41	1.01	3.57	$1.21	0.31%
TAZTIA XT CAP 360MG/24	35	1,320	1,320	12	$1,483.00	1	2.92	$1.12	0.05%
DILTZAC CAP 360MG/24	31	1,250	1,250	10	$1,334.06	1	3.1	$1.07	0.05%
DILTIAZEM CAP 420MG/24	34	1,430	1,430	6	$1,858.65	1	5.67	$1.30	0.07%
DILTIAZEM CAP 120MG CD	359	15,325	13,577	132	$8,617.13	1.13	2.72	$0.63	0.32%
DILTIAZEM CAP 120MG ER	237	11,197	9,417	76	$6,211.64	1.19	3.12	$0.66	0.23%
DILT-CD CAP 120MG	19	690	630	11	$395.73	1.1	1.73	$0.63	0.01%
CARTIA XT CAP 120/24HR	12	541	481	10	$304.07	1.12	1.2	$0.63	0.01%
DILTIAZEM CAP 180MG CD	431	19,383	16,603	107	$13,958.41	1.17	4.03	$0.84	0.51%

DILTIAZEM CAP 180MG ER	301	15,398	11,560	81	$10,874.17	1.33	3.72	$0.94	0.40%
CARTIA XT CAP 180/24HR	26	1,180	1,000	11	$794.65	1.18	2.36	$0.79	0.03%
DILT-CD CAP 180MG	24	1,383	1,083	11	$926.93	1.28	2.18	$0.86	0.03%
DILTIAZEM CAP 240MG CD	599	23,137	21,759	157	$19,852.73	1.06	3.82	$0.91	0.73%
DILTIAZEM CAP 240MG ER	380	16,310	15,155	115	$13,817.43	1.08	3.3	$0.91	0.51%
DILT-CD CAP 240MG	33	1,410	1,410	15	$1,208.35	1	2.2	$0.86	0.04%
CARTIA XT CAP 240/24HR	28	1,315	1,255	18	$1,050.93	1.05	1.56	$0.84	0.04%
DILTIAZEM CAP 300MG CD	80	3,894	3,894	26	$4,148.46	1	3.08	$1.07	0.15%
DILTIAZEM CAP 300MG ER	80	3,727	3,705	28	$3,880.35	1.01	2.86	$1.05	0.14%
DILT-CD CAP 300MG	11	990	990	5	$1,019.93	1	2.2	$1.03	0.04%
CARTIA XT CAP 300/24HR	10	460	430	7	$481.01	1.07	1.43	$1.12	0.02%
CARDIZEM CD CAP 360MG/24	65	2,680	2,680	22	$17,982.75	1	2.95	$6.71	0.66%
CARDIZEM LA TAB 120MG	5	220	205	4	$581.34	1.07	1.25	$2.84	0.02%
CARDIZEM LA TAB 180MG	14	510	480	5	$1,420.88	1.06	2.8	$2.96	0.05%
CARDIZEM LA TAB 240MG	36	1,870	1,450	8	$5,802.80	1.29	4.5	$4.00	0.21%
DILTIAZEM ER TAB 240MG/24	16	694	604	6	$1,916.60	1.15	2.67	$3.17	0.07%
CARDIZEM LA TAB 300MG	10	300	300	1	$1,212.53	1	10	$4.04	0.04%
CARDIZEM LA TAB 360MG	27	1,110	1,110	5	$4,819.03	1	5.4	$4.34	0.18%
DILTIAZEM ER TAB 360MG/24	3	270	270	3	$1,025.66	1	1	$3.80	0.04%
CARDIZEM LA TAB 420MG	11	330	330	2	$1,533.47	1	5.5	$4.65	0.06%
DILTIAZEM ER TAB 420MG/24	1	30	30	1	$126.13	1	1	$4.20	0.00%
FELODIPINE TAB 2.5MG ER	25	725	725	6	$612.33	1	4.17	$0.84	0.02%
FELODIPINE TAB 5MG ER	88	4,080	3,660	22	$3,387.06	1.11	4	$0.93	0.12%
FELODIPINE TAB 10MG ER	227	10,174	9,904	46	$15,099.57	1.03	4.93	$1.52	0.55%
ISRADIPINE CAP 2.5MG	24	1,440	720	3	$1,498.33	2	8	$2.08	0.05%
ISRADIPINE CAP 5MG	14	1,454	615	4	$2,166.37	2.36	3.5	$3.52	0.08%
DYNACIRC CR TAB 5MG	12	1,200	540	4	$3,109.74	2.22	3	$5.76	0.11%
DYNACIRC CR TAB 10MG	41	1,876	1,546	8	$7,478.22	1.21	5.13	$4.84	0.27%
NICARDIPINE CAP 20MG	40	5,730	1,200	7	$786.06	4.78	5.71	$0.66	0.03%
NICARDIPINE CAP 30MG	1	60	30	1	$12.81	2	1	$0.43	0.00%
NIFEDIPINE CAP 10MG	940	63,933	16,344	682	$44,898.18	3.91	1.38	$2.75	1.64%
NIFEDIPINE CAP 20MG	227	15,945	4,620	176	$19,119.94	3.45	1.29	$4.14	0.70%
NIFEDIPINE POW USP	5	33	85	4	$17.96	0.39	1.25	$0.21	0.00%
NIFEDIAC CC TAB 30MG ER	283	11,503	10,193	82	$6,650.55	1.13	3.45	$0.65	0.24%
AFEDITAB TAB 30MG CR	120	3,736	3,646	31	$2,283.61	1.02	3.87	$0.63	0.08%
NIFEDIPINE TAB 30MG ER	114	5,283	5,198	41	$3,063.60	1.02	2.78	$0.59	0.11%
NIFEDIAC CC TAB 60MG ER	234	9,965	8,955	54	$11,324.57	1.11	4.33	$1.26	0.41%
NIFEDIPINE TAB 60MG ER	151	6,201	5,781	37	$6,968.44	1.07	4.08	$1.21	0.25%
AFEDITAB TAB 60MG CR	106	4,392	4,062	31	$4,955.25	1.08	3.42	$1.22	0.18%
ADALAT CC TAB 60MG ER	5	195	195	2	$490.65	1	2.5	$2.52	0.02%
NIFEDIAC CC TAB 90MG ER	103	3,920	3,590	20	$7,154.83	1.09	5.15	$1.99	0.26%

ADALAT CC TAB 90MG ER	11	330	330	2	$992.68	1	5.5	$3.01	0.04%
NIFEDIPINE TAB 30MG ER	950	38,255	33,165	348	$24,362.95	1.15	2.73	$0.73	0.89%
NIFEDICAL XL TAB 30MG	578	25,047	19,289	283	$15,637.42	1.3	2.04	$0.81	0.57%
NIFEDIPINE TAB 60MG ER	772	34,490	28,180	260	$32,463.04	1.22	2.97	$1.15	1.19%
NIFEDICAL XL TAB 60MG	645	27,873	21,937	189	$26,315.87	1.27	3.41	$1.20	0.96%
NIFEDIPINE TAB 90MG ER	810	36,780	33,680	201	$43,883.83	1.09	4.03	$1.30	1.61%
SULAR TAB 8.5MG	6	180	180	1	$606.37	1	6	$3.37	0.02%
SULAR TAB 17MG	3	97	70	2	$354.03	1.39	1.5	$5.06	0.01%
SULAR TAB 34MG	2	200	200	1	$931.25	1	2	$4.66	0.03%
VERAPAMIL TAB 40MG	81	5,450	2,546	27	$1,499.18	2.14	3	$0.59	0.05%
VERAPAMIL TAB 80MG	324	20,602	10,680	87	$2,602.66	1.93	3.72	$0.24	0.10%
VERAPAMIL TAB 120MG	399	23,567	13,431	107	$3,471.17	1.75	3.73	$0.26	0.13%
VERAPAMIL TAB 120MG ER	360	17,868	15,513	118	$6,371.91	1.15	3.05	$0.41	0.23%
VERAPAMIL TAB 120MG SR	41	1,530	1,380	18	$544.97	1.11	2.28	$0.39	0.02%
VERAPAMIL TAB 180MG ER	417	20,325	16,740	110	$6,671.77	1.21	3.79	$0.40	0.24%
VERAPAMIL TAB 180MG SR	54	2,575	2,170	15	$861.76	1.19	3.6	$0.40	0.03%
VERAPAMIL TAB 240MG ER	1,252	56,361	50,370	328	$18,124.10	1.12	3.82	$0.36	0.66%
VERAPAMIL TAB 240MG SR	225	10,244	9,783	75	$3,334.86	1.05	3	$0.34	0.12%
VERAPAMIL CAP 100MG ER	12	620	620	9	$765.30	1	1.33	$1.23	0.03%
VERAPAMIL CAP 120MG ER	187	8,532	6,927	62	$4,141.10	1.23	3.02	$0.60	0.15%
VERAPAMIL CAP 120MG SR	32	1,990	1,304	10	$976.46	1.53	3.2	$0.75	0.04%
VERAPAMIL CAP 180MG ER	118	5,459	4,544	35	$2,636.28	1.2	3.37	$0.58	0.10%
VERAPAMIL CAP 180MG SR	16	750	600	4	$342.96	1.25	4	$0.57	0.01%
VERAPAMIL CAP 200MG ER	50	1,595	1,595	7	$2,296.22	1	7.14	$1.44	0.08%
VERAPAMIL CAP 240MG ER	215	8,995	8,635	58	$4,769.22	1.04	3.71	$0.55	0.17%
VERAPAMIL CAP 240MG SR	31	1,110	1,110	9	$631.64	1	3.44	$0.57	0.02%
VERAPAMIL CAP 300MG ER	18	952	641	6	$1,836.40	1.49	3	$2.86	0.07%
VERAPAMIL CAP 360MG SR	109	4,860	4,860	27	$7,688.48	1	4.04	$1.58	0.28%
COVERA-HS TAB 180MG	7	210	210	1	$395.41	1	7	$1.88	0.01%
COVERA-HS TAB 240MG	5	150	150	1	$393.28	1	5	$2.62	0.01%
CLASS SUBTOTAL	**41,111**	**2,695,429**	**1,523,473**	**1,517**	**$747,255.40**	**1.30**	**3.44**	**$1.47**	
CCB/ACE INHIBITOR COMBINATION PRODUCTS									
AMLOD/BENAZP CAP 2.5-10MG	33	1,860	1,860	6	$3,148.69	1	5.5	$1.69	0.12%
AMLOD/BENAZP CAP 5-10MG	236	11,220	9,430	44	$19,081.80	1.19	5.36	$2.02	0.70%
AMLOD/BENAZP CAP 5-20MG	400	21,589	17,469	82	$37,923.23	1.24	4.88	$2.17	1.39%
LOTREL CAP 5-40MG	77	3,610	3,315	13	$13,183.31	1.09	5.92	$3.98	0.48%
AMLOD/BENAZP CAP 10-20MG	648	29,758	27,665	133	$59,817.07	1.08	4.87	$2.16	2.19%
LOTREL CAP 10-20MG	10	600	300	1	$2,394.98	2	10	$7.98	0.09%
LOTREL CAP 10-40MG	308	13,787	13,197	60	$60,874.83	1.04	5.13	$4.61	2.23%
TARKA TAB 1-240 CR	2	180	180	1	$527.00	1	2	$2.93	0.02%
TARKA TAB 2-180 CR	12	729	729	2	$2,127.56	1	6	$2.92	0.08%

TARKA TAB 2-240 CR	48	2,337	2,337	11	$6,750.90	1	4.36	$2.89	0.25%
TARKA TAB 4-240 CR	70	3,640	3,080	13	$9,914.74	1.18	5.38	$3.22	0.36%
CLASS SUBTOTAL	**1,844**	**89,310**	**79,652**	**366**	**$215,744.00**	**1.17**	**5.40**	**$3.33**	
CCB/ARB COMBINATIONS									
EXFORGE TAB 10-320MG	283	8,445	8,447	51	$33,564.59	1	5.55	$3.97	
EXFORGE TAB 5-160MG	161	4,830	4,830	27	$13,614.24	1	5.96	$2.82	
EXFORGE TAB 5-320MG	102	3,060	3,060	24	$10,920.76	1	4.25	$3.57	
EXFORGE TAB 10-160MG	78	2,337	2,337	15	$7,389.17	1	5.2	$3.16	
AZOR TAB 10-40MG	50	1,620	1,620	7	$6,159.62	1	7.14	$3.80	
AZOR TAB 10-20MG	9	480	270	2	$1,439.93	1.78	4.5	$5.33	
AZOR TAB 5-40MG	9	270	270	3	$950.04	1	3	$3.52	
AZOR TAB 5-20MG	2	200	200	1	$551.02	1	2	$2.76	
CLASS SUBTOTAL	**694**	**21,242**	**21,034**	**122**	**$74,589.37**	**1.01**	**5.69**	**$3.55**	
ACE INHIBITORS									
ENALAPRIL TAB 10MG	3,270	170,195	120,618	836	$20,695.61	1.41	3.91	$0.17	0.76%
ENALAPRIL TAB 20MG	3,182	177,008	117,350	745	$22,737.28	1.51	4.27	$0.19	0.83%
ENALAPRILAT INJ 1.25/ML	1	1	30	1	$6.21	0.02	1	$0.21	0.00%
FOSINOPRIL TAB 10MG	294	12,161	11,773	68	$3,333.59	1.03	4.32	$0.28	0.12%
FOSINOPRIL TAB 20MG	536	26,553	24,678	140	$7,184.23	1.08	3.83	$0.29	0.26%
FOSINOPRIL TAB 40MG	285	14,529	13,479	84	$4,104.60	1.08	3.39	$0.30	0.15%
LISINOPRIL TAB 2.5MG	1,928	75,577	72,207	544	$9,283.28	1.05	3.54	$0.13	0.34%
LISINOPRIL TAB 5MG	6,090	249,024	238,255	1,757	$32,122.50	1.05	3.47	$0.13	1.18%
LISINOPRIL TAB 10MG	16,137	673,029	627,667	4,807	$95,096.52	1.07	3.36	$0.15	3.48%
ZESTRIL TAB 10MG	13	780	390	1	$1,127.14	2	13	$2.89	0.04%
PRINIVIL TAB 10MG	8	248	248	1	$269.72	1	8	$1.09	0.01%
LISINOPRIL TAB 20MG	16,565	748,687	644,368	4,826	$107,260.88	1.16	3.43	$0.17	3.92%
PRINIVIL TAB 20MG	2	60	60	1	$66.76	1	2	$1.11	0.00%
LISINOPRIL TAB 30MG	791	32,384	27,402	205	$7,263.78	1.18	3.86	$0.27	0.27%
LISINOPRIL TAB 40MG	8,370	369,408	329,579	2,108	$82,922.61	1.12	3.97	$0.25	3.03%
LISINOPRIL 40MG TAB	5	150	150	1	$27.99	1	5	$0.19	0.00%
MOEXIPRIL TAB 7.5MG	19	570	570	2	$282.61	1	9.5	$0.50	0.01%
MOEXIPRIL TAB 15MG	33	1,587	1,527	8	$728.37	1.04	4.13	$0.48	0.03%
ACEON TAB 4MG	14	560	560	2	$1,265.21	1	7	$2.26	0.05%
PERINDOPRIL TAB 4MG	5	335	335	2	$563.63	1	2.5	$1.68	0.02%
ACEON TAB 8MG	11	330	330	1	$909.14	1	11	$2.75	0.03%
QUINAPRIL TAB 5MG	34	1,170	1,140	8	$303.60	1.03	4.25	$0.27	0.01%
QUINAPRIL TAB 10MG	256	10,612	9,442	59	$2,627.19	1.12	4.34	$0.28	0.10%
QUINAPRIL TAB 20MG	424	21,678	17,432	97	$4,921.07	1.24	4.37	$0.28	0.18%
QUINAPRIL TAB 40MG	472	24,402	20,354	103	$5,514.65	1.2	4.58	$0.27	0.20%
ACCUPRIL TAB 40MG	1	30	30	1	$55.22	1	1	$1.84	0.00%
RAMIPRIL CAP 1.25MG	4	240	240	3	$57.42	1	1.33	$0.24	0.00%
RAMIPRIL CAP 2.5MG	205	9,872	9,182	58	$2,130.59	1.08	3.53	$0.23	0.08%

RAMIPRIL CAP 5MG	360	15,896	13,197	90	$3,600.90	1.2	4	$0.27	0.13%
RAMIPRIL CAP 10MG	425	21,536	17,791	105	$4,737.45	1.21	4.05	$0.27	0.17%
ALTACE CAP 10MG	2	180	180	1	$471.17	1	2	$2.62	0.02%
TRANDOLAPRIL TAB 1MG	7	390	340	2	$98.90	1.15	3.5	$0.29	0.00%
TRANDOLAPRIL TAB 2MG	23	690	690	4	$253.21	1	5.75	$0.37	0.01%
TRANDOLAPRIL TAB 4MG	23	870	870	6	$418.44	1	3.83	$0.48	0.02%
CLASS SUBTOTAL	**59,795**	**2,660,742**	**2,322,464**	**16,677**	**$422,441.47**	**1.09**	**4.44**	**0.68**	
ACE/HCTZ COMBINATIONS									
BENAZEP/HCTZ TAB 5-6.25	6	390	390	2	$113.96	1	3	$0.29	0.00%
BENAZEP/HCTZ TAB 10-12.5	98	4,740	4,230	23	$1,260.86	1.12	4.26	$0.30	0.05%
BENAZEP/HCTZ TAB 20-12.5	212	10,124	8,634	58	$2,743.97	1.17	3.66	$0.32	0.10%
BENAZEP/HCTZ TAB 20-25MG	236	11,705	9,405	54	$3,139.44	1.24	4.37	$0.33	0.11%
CAPTOPR/HCTZ TAB 25-15MG	67	4,146	2,388	12	$856.97	1.74	5.58	$0.36	0.03%
CAPTOPR/HCTZ TAB 25-25MG	41	2,430	1,530	8	$482.69	1.59	5.13	$0.32	0.02%
CAPTOPR/HCTZ TAB 50-15MG	9	780	450	4	$175.90	1.73	2.25	$0.39	0.01%
CAPTOPR/HCTZ TAB 50-25MG	108	5,764	4,209	19	$1,393.53	1.37	5.68	$0.33	0.05%
ENALAPR/HCTZ TAB 5-12.5MG	183	7,040	6,670	46	$1,365.18	1.06	3.98	$0.20	0.05%
ENALAPR/HCTZ TAB 10-25MG	519	25,695	22,957	126	$6,020.42	1.12	4.12	$0.26	0.22%
FOSINOP/HCTZ TAB 10/12.5	11	690	690	5	$523.22	1	2.2	$0.76	0.02%
FOSINOP/HCTZ TAB 20/12.5	27	1,140	810	4	$1,095.79	1.41	6.75	$1.35	0.04%
LISINOP/HCTZ TAB 10-12.5	2,807	118,825	113,495	940	$22,992.20	1.05	2.99	$0.20	0.84%
LISINOP/HCTZ TAB 20-12.5	5,537	272,601	217,114	1,606	$50,353.40	1.26	3.45	$0.23	1.84%
LISINOP/HCTZ TAB 20-25MG	6,080	261,009	248,521	1,847	$53,146.80	1.05	3.29	$0.21	1.94%
MOEXIPR/HCTZ TAB 7.5-12.5	10	300	300	1	$207.49	1	10	$0.69	0.01%
MOEXIPR/HCTZ TAB 15-12.5	2	60	60	2	$34.20	1	1	$0.57	0.00%
MOEXIPR/HCTZ TAB 15-25MG	24	870	870	6	$576.82	1	4	$0.66	0.02%
QNAPRIL/HCTZ TAB 10-12.5	10	360	360	2	$290.17	1	5	$0.81	0.01%
QNAPRIL/HCTZ TAB 20-12.5	54	2,824	1,976	15	$2,174.22	1.43	3.6	$1.10	0.08%
QNAPRIL/HCTZ TAB 20-25MG	36	1,470	1,440	13	$1,205.81	1.02	2.77	$0.84	0.04%
CLASS SUBTOTAL	**16,077**	**732,963**	**646,499**	**4,793**	**$150,153.04**	**1.21**	**4.14**	**$0.50**	
ARBs									
DIOVAN TAB 40MG	155	6,941	5,481	37	$13,536.37	1.27	4.19	$2.47	0.50%
DIOVAN TAB 80MG	602	26,329	24,179	135	$62,420.45	1.09	4.46	$2.58	2.28%
DIOVAN TAB 160MG	603	28,141	24,983	169	$71,677.42	1.13	3.57	$2.87	2.62%
DIOVAN TAB 320MG	366	14,138	14,138	85	$44,257.01	1	4.31	$3.13	1.62%
ATACAND TAB 4MG	21	1,570	800	3	$3,327.81	1.96	7	$4.16	0.12%
ATACAND TAB 8MG	51	2,370	2,370	10	$5,087.92	1	5.1	$2.15	0.19%
ATACAND TAB 16MG	32	1,830	1,560	7	$3,903.19	1.17	4.57	$2.50	0.14%
ATACAND TAB 32MG	97	5,450	5,150	20	$15,145.62	1.06	4.85	$2.94	0.55%

TEVETEN TAB 600MG	3	270	270	1	$785.48	1	3	$2.91	0.03%
AVAPRO TAB 75MG	65	2,250	2,250	16	$4,927.09	1	4.06	$2.19	0.18%
AVAPRO TAB 150MG	470	20,767	20,004	125	$47,722.29	1.04	3.76	$2.39	1.75%
AVAPRO TAB 300MG	454	18,854	18,794	101	$52,079.34	1	4.5	$2.77	1.91%
COZAAR TAB 25MG	59	3,284	2,582	19	$5,482.31	1.27	3.11	$2.12	0.20%
LOSARTAN POT TAB 25MG	14	700	610	9	$939.82	1.15	1.56	$1.54	0.03%
COZAAR TAB 50MG	269	14,245	11,446	69	$31,291.27	1.24	3.9	$2.73	1.14%
LOSARTAN POT TAB 50MG	52	2,600	2,080	33	$5,105.29	1.25	1.58	$2.45	0.19%
COZAAR TAB 100MG	285	13,682	13,237	64	$38,596.73	1.03	4.45	$2.92	1.41%
LOSARTAN POT TAB 100MG	48	2,402	2,372	32	$6,303.61	1.01	1.5	$2.66	0.23%
BENICAR TAB 5MG	17	660	720	9	$1,241.31	0.92	1.89	$1.72	0.05%
BENICAR TAB 20MG	392	15,433	14,998	91	$32,418.52	1.03	4.31	$2.16	1.19%
BENICAR TAB 40MG	276	10,680	10,530	67	$28,651.54	1.01	4.12	$2.72	1.05%
MICARDIS TAB 20MG	188	6,490	6,490	41	$17,483.02	1	4.59	$2.69	0.64%
MICARDIS TAB 40MG	630	23,309	23,083	145	$63,706.25	1.01	4.34	$2.76	2.33%
MICARDIS TAB 80MG	642	22,664	22,806	148	$62,636.16	0.99	4.34	$2.75	2.29%
CLASS SUBTOTAL	**5,791**	**245,059**	**230,806**	**1,436**	**$618,725.82**	**1.11**	**3.88**	**$2.60**	
ARB/HCTZ COMBINATIONS									
ATACAND HCT TAB 16-12.5	23	890	890	5	$2,559.03	1	4.6	$2.88	0.09%
ATACAND HCT TAB 32-12.5	91	3,631	3,631	15	$10,146.37	1	6.07	$2.79	0.37%
TEVETEN HCT TAB 600-12.5	5	390	390	2	$1,190.02	1	2.5	$3.05	0.04%
AVALIDE TAB 150-12.5	339	12,973	12,518	56	$35,263.23	1.04	6.05	$2.82	1.29%
AVALIDE TAB 300-12.5	161	6,930	6,930	33	$21,004.66	1	4.88	$3.03	0.77%
AVALIDE TAB 300-25MG	205	8,310	8,385	42	$27,724.59	0.99	4.88	$3.31	1.01%
HYZAAR TAB 50-12.5	239	11,320	9,980	45	$27,440.38	1.13	5.31	$2.75	1.00%
LOSARTAN/HCT TAB 50-12.5	46	2,250	1,740	25	$4,851.42	1.29	1.84	$2.79	0.18%
HYZAAR TAB 100-12.5	19	890	950	9	$2,933.38	0.94	2.11	$3.09	0.11%
LOSARTAN/HCT TAB 100-12.5	3	90	90	1	$272.94	1	3	$3.03	0.01%
HYZAAR TAB 100-25	454	21,608	21,392	106	$70,850.08	1.01	4.28	$3.31	2.59%
LOSARTAN/HCT TAB 100-25	73	3,696	3,666	50	$10,912.14	1.01	1.46	$2.98	0.40%
BENICAR HCT TAB 20-12.5	175	7,600	7,600	45	$18,393.39	1	3.89	$2.42	0.67%
BENICAR HCT TAB 40-12.5	156	7,044	7,044	37	$19,867.07	1	4.22	$2.82	0.73%
BENICAR HCT TAB 40-25MG	376	17,427	17,142	83	$54,324.12	1.02	4.53	$3.17	1.99%
MICARDIS HCT TAB 40/12.5	152	5,250	5,190	35	$14,453.24	1.01	4.34	$2.78	0.53%
MICARDIS HCT TAB 80/12.5	169	6,960	6,150	45	$19,307.46	1.13	3.76	$3.14	0.71%
MICARDIS HCT TAB 80/25MG	203	7,514	7,514	42	$21,131.17	1	4.83	$2.81	0.77%
DIOVAN HCT TAB 80/12.5	237	9,490	9,430	51	$23,660.27	1.01	4.65	$2.51	0.87%
DIOVAN HCT TAB 160/12.5	401	16,766	16,011	102	$46,244.41	1.05	3.93	$2.89	1.69%
DIOVAN HCT TAB 160/25MG	474	20,268	18,839	97	$62,905.47	1.08	4.89	$3.34	2.30%
DIOVAN HCT TAB 320/12.5	130	5,960	5,960	32	$20,891.76	1	4.06	$3.51	0.76%
DIOVAN HCT TAB 320/25MG	236	9,948	9,896	56	$39,543.87	1.01	4.21	$4.00	1.45%
CLASS SUBTOTAL	**4,367**	**187,205**	**181,338**	**1,014**	**$555,870.47**	**1.03**	**4.10**	**$3.01**	

DIRECT RENIN INHIBITORS									
VALTURNA TAB 300-320	2	180	180	2	$543.02	1	1	$3.02	0.02%
TEKTURNA TAB 150MG	76	2,910	2,700	15	$7,344.96	1.08	5.07	$2.72	0.27%
TEKTURNA TAB 300MG	105	4,780	4,960	26	$15,173.89	0.96	4.04	$3.06	0.56%
CLASS SUBTOTAL	**183**	**7,870**	**7,840**	**43**	**$23,061.87**	**1.01**	**3.37**	**$2.93**	
CATEGORY TOTALS	**129,862**	**6,639,820**	**5,013,106**	**25,919***	**$2,807,841.44**	**1.32**	**5.01**	**$0.56**	

Total unduplicated number of members

PRODUCT DETAILS OF TRIBENZOR™ (OLMESARTAN, AMLODIPINE, HCTZ)

INDICATIONS:
Tribenzor® is a combination of an angiotensin 2 receptor blocker, a dihydropyridine calcium channel blocker, and a thiazide diuretic indicated for the treatment of hypertension. Tribenzor® is not indicated for initial therapy.

DOSAGE FORMS: Tablets of olmesartan medoxomil/amlodipine/hydrochlorothiazide:

- 20/5/12.5 mg
- 40/5/12.5 mg
- 40/5/25 mg
- 40/10/12.5 mg
- 40/10/25 mg

ADMINISTRATION:

- Tribenzor® may be substituted for its individually titrated components for patients on olmesartan medoxomil, amlodipine, and hydrochlorothiazide.
- Tribenzor® may be used as add-on/switch therapy to provide additional blood pressure lowering for patients not adequately controlled on agents from two of the following antihypertensive classes: angiotensin receptor blockers, calcium channel blockers, and diuretics at their maximally tolerated, labeled, or usual dose.
- Dosage may be increased after 2 weeks to a maximum dose of 40/10/25 mg once daily, usually by increasing one component at a time.

CONTRAINDICATIONS: Anuria; Hypersensitivity to sulfonamide-derived drugs

SPECIAL POPULATIONS:

- Pregnancy: Avoid use in pregnancy.
- Nursing mothers: Avoid use while nursing; discontinue either nursing or the drug.
- Geriatric patients: No overall differences in the efficacy or safety of Tribenzor® were observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

WARNINGS & PRECAUTIONS:

- Avoid fetal or neonatal exposure
- Hypotension in volume- or salt-depleted patients with treatment initiation may occur
- Correct volume-depletion prior to administration
- Increased angina or myocardial infarction with calcium channel blockers may occur
- upon dosage initiation or increase
- Avoid in patients with severely impaired renal function (creatinine clearance ≤30 mL/min)
- Withhold or discontinue Tribenzor® if progressive renal impairment becomes evident
- Thiazides should be used with caution in patients with mildly to moderately impaired hepatic function or progressive liver disease. Avoid in patients with severely impaired hepatic function
- Observe for signs of fluid or electrolyte imbalance
- Thiazide diuretics may cause an exacerbation or activation of systemic lupus erythematosus

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

- dizziness
- peripheral edema
- headache
- fatigue
- nasopharyngitis
- muscle spasms
- nausea
- upper respiratory tract infection
- diarrhea
- urinary tract infection
- joint swelling

DRUG INTERACTIONS:

- Alcohol, barbiturates, narcotics: Potentiation of orthostatic hypotension.
- Anti-diabetic drugs: Dosage adjustment of antidiabetic may be required.
- Cholestyramine and colestipol: Reduced absorption of thiazides.
- Corticosteroids, ACTH: Electrolyte depletion, hypokalemia.
- Lithium: Reduced renal clearance and high risk of lithium toxicity when used with diuretics. Should not be given with diuretics.
- NSAIDs: Can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

PRODUCT DETAILS OF TEKAMLO™ (ALISKIREN and AMLODIPINE)

INDICATIONS: Tekamlo® is indicated

- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.
- In patients not adequately controlled with monotherapy.
- As a substitute for its titrated components.

DOSAGE FORMS: Tablets (aliskiren/amlodipine): 150mg/5mg, 150mg/10mg, 300mg/5mg, 300mg/10mg

ADMINISTRATION:

- **Add-on therapy or initial therapy**: Initiate with 150 mg/5 mg. Titrate as needed up to a maximum of 300mg/10mg.
- **Replacement therapy**: may substitute for titrated components.
- The blood pressure lowering effect is largely attained within 1-2 weeks.
- Administer one tablet daily with a routine pattern with regard to meals.
- May administer with other antihypertensive agents.
- Additive effects with ACE inhibitors at maximal doses have not been studied.

CONTRAINDICATIONS: None listed.

SPECIAL POPULATIONS:

- **Pregnancy Category D:** The use of drugs that act directly on the renin-angiotensin-aldosterone system during the second and third trimesters of pregnancy can cause fetal and neonatal morbidity and death.
- **Nursing Mothers:** Discontinue drug or nursing.
- **Pediatric:** Safety and effectiveness of Tekamlo® in pediatric patients have not been established.
- **Geriatric:** In the short-term controlled clinical trials of Tekamlo, 17% of patients treated with Tekamlo® were ≥ 65 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

WARNINGS & PRECAUTIONS:

- Avoid fetal and neonatal exposure.
- Head and neck angioedema: Discontinue Tekamlo and monitor until signs and symptoms resolve.
- Hypotension in volume- and/or salt-depleted patients: Correct imbalances before initiating therapy with Tekamlo.
- Increased angina or myocardial infarction with calcium channel blockers may occur upon dosage initiation or increase.
- Patients with renal impairment: Decrease in renal function may be anticipated with susceptible individuals.
- Patients with hepatic impairment: Titrate slowly.
- Patients with heart failure: Titrate slowly.
- Hyperkalemia: Monitor serum potassium when co-administering with ACEI, potassium-sparing diuretics, potassium supplements, or other potassium-containing salt substitutes.

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

DRUG INTERACTIONS: Cyclosporine or itraconazole: Concomitant use is not recommended.

PRODUCT DETAILS OF NEXICLON XR® (CLONIDINE EXTENDED-RELEASE)

INDICATIONS: Nexiclon XR® is indicated in the treatment of hypertension. Nexiclon XR® may be used alone or concomitantly with other antihypertensive agents.

DOSAGE FORMS: Extended-Release Tablets: 0.17, 0.26 mg clonidine base.

DOSING & ADMINISTRATION: The dose of Nexiclon XR® must be adjusted according to the patient's individual blood pressure response. The following is a general guide to its administration in adults.

Initial Dose
Dosing with Nexiclon XR® should be initiated at 0.17 mg once daily. Elderly patients may benefit from a lower initial dose. Initial dose is recommended to be administered at bedtime.

Maintenance Dose
Further increments of 0.09 mg once daily may be made at weekly intervals if necessary until the desired response is achieved. The therapeutic doses most commonly employed have ranged from 0.17 mg to 0.52 mg once daily. Nexiclon XR® was studied at doses of 0.17 to 0.52 mg once daily. Doses higher than 0.52 mg per day were not evaluated and are not recommended.

Patients Currently Using Clonidine Hydrochloride Immediate-Release Tablets
The recommended dose of Nexiclon XR® for patients who are currently taking clonidine hydrochloride immediate-release tablets is provided in the table below:

	Nexiclon XR® (clonidine) Extended-Release Tablets	**Equivalent Dose of Clonidine HCl Immediate-Release Tablets**
Initial Dose	0.17 mg once daily	0.1 mg twice daily
Maintenance Dose Titration Increments	0.09 mg once daily	0.05 mg twice daily
Common Doses Used for Blood Pressure Effect	0.17 mg once daily	0.1 mg twice daily
	0.34 mg once daily	0.2 mg twice daily
	0.52 mg once daily	0.3 mg twice daily

Renal Impairment
Adjust dosage according to the degree of impairment. In patients with end-stage kidney disease on maintenance dialysis, start at 0.09 mg per day and up-titrate slowly to minimize dose related adverse events. Monitor patients carefully, especially for bradycardia, sedation and hypotension. Only a minimal amount of clonidine is removed during routine hemodialysis.
In patients with moderate to severe kidney impairment not undergoing dialysis, initiate clonidine at the same dose as for patients without renal impairment. Up-titrate slowly and monitor for dose-related adverse events.

CONTRAINDICATIONS: Nexiclon XR® should not be used in patients with known hypersensitivity to clonidine.

SPECIAL POPULATIONS:
- Pregnancy Category C
- Nursing Mothers: Clonidine is secreted in human milk.
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

- Geriatric Use: Elderly patients may benefit from a lower initial dose.
- Patients with renal impairment: The initial dosage should be based on the degree of impairment. Monitor patients carefully for hypotension and bradycardia, and titrate to higher doses cautiously. Only a minimal amount of clonidine is removed during routine hemodialysis.

WARNINGS & PRECAUTIONS:

- **Withdrawal:** Instruct patients not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with Nexiclon XR®, reduce the dose gradually over 2 to 4 days to avoid withdrawal symptoms.
    - An excessive rise in blood pressure following discontinuation of Nexiclon XR® can be reversed by administration of oral clonidine hydrochloride or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of Nexiclon XR®.
    - **Because children commonly have gastrointestinal illnesses that lead to vomiting, they may be particularly susceptible to hypertensive episodes resulting from abrupt inability to take medication.**
- **General Precautions:** In patients who have developed localized contact sensitization to a clonidine transdermal system, substitution of oral clonidine therapy may be associated with the development of a generalized skin rash. In patients who develop an allergic reaction to a clonidine transdermal system, substitution of oral clonidine may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema). Monitor carefully and up-titrate slowly in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. The sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.
- **Perioperative Use:** Nexiclon XR® may be administered up to 28 hours prior to surgery and resumed the following day. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required.

ADVERSE REACTIONS

- The following serious adverse reactions are discussed in detail elsewhere in the labeling:
    - Withdrawal
    - Allergic reactions
- **Nexiclon XR® Clinical Trial Experience:** There is very limited experience with Nexiclon XR®. In controlled trials. Based on this limited experience, the adverse event profile appears similar to the immediate-release clonidine formulation.
- **Experience with Immediate-Release Clonidine:** Most adverse reactions are mild and tend to diminish with continued therapy. The most frequent (which also appear to be dose-related) are dry mouth (approximately 40%); drowsiness (approximately 33%); dizziness (approximately 16%); constipation and sedation (approximately 10% each).

  The following less frequent adverse reactions have also been reported in patients receiving immediate-release clonidine, but in many cases patients were receiving concomitant medication and a causal relationship has not been established.
    - Body as a Whole: Fatigue, fever, headache, pallor, weakness, and withdrawal syndrome. Also reported were a weakly positive Coombs' test and increased sensitivity to alcohol.
    - Cardiovascular: Bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

- Central Nervous System (CNS): Agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares.
- Dermatological: Alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.
- Gastrointestinal: Abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, and vomiting.
- Genitourinary: Decreased sexual activity, difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention.
- Hematologic: Thrombocytopenia
- Metabolic: Gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, and weight gain.
- Musculoskeletal: Leg cramps and muscle or joint pain.
- Oro-otolaryngeal: Dryness of the nasal mucosa.
- Ophthalmological: Accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of eyes.

DRUG INTERACTIONS:

- No drug interaction studies have been conducted with Nexiclon XR®. The following have been reported with other oral formulations of clonidine:
  - Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. If a patient receiving clonidine hydrochloride is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.
  - Monitor heart rate in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction, e.g., digitalis, calcium channel blockers, and beta-blockers. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.
  - Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.
  - **Alcohol:** Based on *in vitro* studies, high concentration of alcohol may increase the rate of release of Nexiclon XR®.

INFORMATION FOR PATIENTS

- Caution patients against interruption of Nexiclon XR® therapy without their healthcare provider's advice.
- Advise patients who engage in potentially hazardous activities, such as operating machinery or driving, of a possible sedative effect of clonidine. The sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

REFERENCES

1. **Tribenzor® Label Information. Daiichi Sankyo, Inc**. Available online at: http://www.tribenzor.com/pdf/TRIBENZOR_PI.pdf. Last revised July 2010
2. **Tekamlo® Label Information. Novartis Pharmaceuticals Corporation**. Available online at: http://www.pharma.us.novartis.com/product/pi/pdf/tekamlo.pdf. Last revised September 2010.
3. **Nexiclon XR® Label Information. NextWave Pharmaceuticals, Inc**. Available online at http://www.nextwavepharma.com/pi/nexiclonxr_tablets_102010.pdf. Last revised October 2010.

Appendix H

FISCAL YEAR 2010 ANNUAL REVIEW OF ADHD MEDICATIONS AND 30 DAY NOTICE TO PRIOR AUTHORIZE KAPVAY® (CLONIDINE EXTENDED RELEASE) AND XYREM® (SODIUM OXYBATE)

OKLAHOMA HEALTH CARE AUTHORITY
JANUARY 2011

2010 PRIOR AUTHORIZATION CRITERIA

Tier 1	Tier 2	Tier 3
Amphetamine	**Amphetamine**	**Amphetamine**
Adderall®	Adderall XR®	Desoxyn®
Methylphenidate	Vyvanse®	Dexedrine®
Ritalin®	**Methylphenidate**	Dexedrine Spansules®
Methylin®	Metadate ER®	ProCentra™ Oral Solution
Ritalin SR®	Metadate CD®	**Methylphenidate**
Concerta®	Ritalin LA®	Daytrana™ Patch
Focalin®	**Non-Stimulant**	**Non-Stimulant**
Focalin XR®	Intuniv®	Provigil®
	Strattera®	Nuvigil®

Tiers based on Supplemental Rebate Participation.
Mandatory Generic Plan Applies.

For Tier 2 Products:

1. Trial with <u>one</u> Tier 1 drug (should include a longer-acting product).
   a. Trial should have been within the last 30 days.
   b. Dosing up to maximum or provide information regarding side effects at higher dose.
   c. If trial is 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.
2. Diagnosis of ADHD or Narcolepsy.
3. Clinical exception for non-stimulants if tics or substance abuse is present.
4. Only use of one long-acting product (regardless of tier level) is allowed concurrently – except for a maximum of a two month titration period.
5. An immediate release product of the same drug type may be used concurrently if an afternoon dose is required.

For Tier 3 Products:

1. Trial with <u>one</u> Tier 1 drug and <u>one</u> Tier 2 drug **OR** two trials of either a Tier 1 or Tier 2.
   a. Both trials should have been within the last 60 days.
   b. Dosing of Tier 1 up to the FDA maximum or provide information regarding side effects at higher dose.
   c. If trials are not in members 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.
2. Diagnosis of ADHD or Narcolepsy.
3. All other Tier 2 criteria apply.

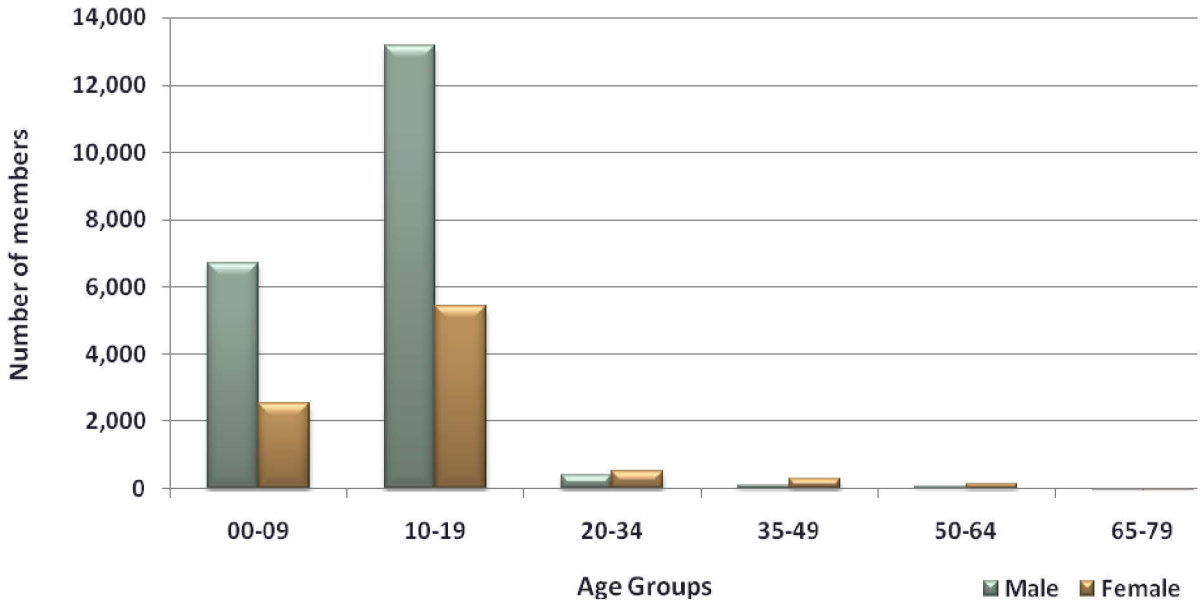
For all Tiers:

1. Dosing cannot exceed 1.5 times the FDA maximum.
2. Prior Authorization is required for all tiers for members greater than 20 years of age. Must have a diagnosis of ADHD or Narcolepsy.

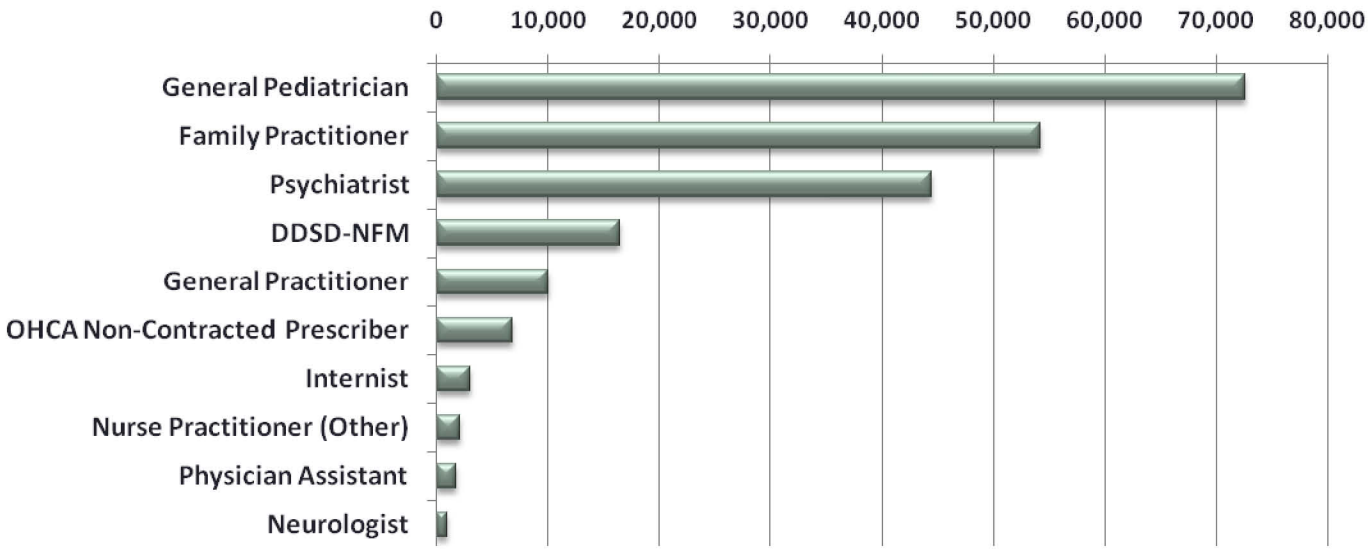
Fiscal Year Comparison

Fiscal Year	Members	Claims	Paid	Paid/Claim	Perdiem	Units	Days
2009	26,405	192,301	$22,190,870.33	$115.40	$3.87	6,915,600	5,734,094
2010	29,425	215,846	$26,001,321.94	$120.46	$4.05	7,591,802	6,425,500
% Change	11.40%	12.20%	17.20%	4.40%	4.70%	9.80%	12.10%
Change	3,020	23,545	$3,810,451.61	$5.06	$0.18	676,202	691,406

Demographics of Members during FY 2010



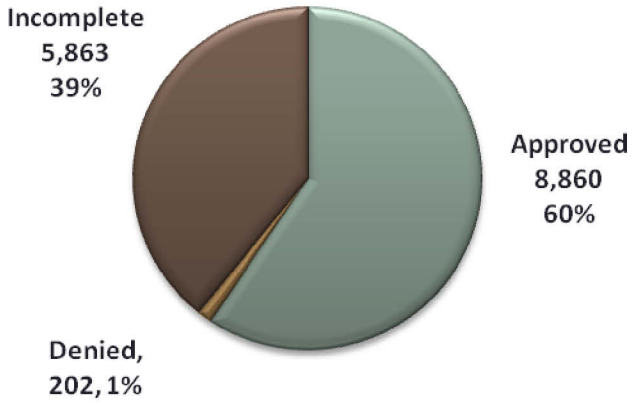
Top Prescribers by Number of Claims for FY 2010



PRIOR AUTHORIZATION OF ADHD/NARCOLEPSY MEDICATIONS

There were a total of 14,925 petitions submitted for this PBPA category during fiscal year 2010. Computer edits are in place to detect tier-1 medications in member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.

Status of Petitions during FY 2010



MARKET NEWS AND UPDATE

Anticipated Patent Expirations

- **Concerta® (methylphenidate extended release) –** On April 26, 2010 the Court of Appeals for the Federal Circuit has denied an appeal by McNeil Pediatrics, a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., to overturn a 2009 decision by the U.S. District Court of Delaware that the patent for Concerta® (methylphenidate HCl) Extended-Release Tablets CII is invalid and not infringed by Andrx Corporation. The generic version is expected as early as middle of 2011.[1]
- **Focalin XR® (dexmethylphenidate)** – anticipated to expire 2015.[2]
- **Strattera® (atomoxetine)** – anticipated to expire 2016.[3]
- **Metadate CD® (methylphenidate extended release)** - anticipated to expire 2020.[4]
- **Ritalin LA® (methylphenidate extended release)** – anticipated to expire 2015.[5]
- **Provigil® (modafinil)** - anticipated to expire 2014.[6]

Clonidine Extended Release – On October 7, 2010 the US Food and Drug Administration (FDA) approved Kapvay® (clonidine hydrochloride extended release) manufactured by Shionogi Inc. Kapvay® is indicated to be used alone or with stimulants for the treatment ADHD in pediatric patients aged 6 to 17 years. Although Kapvay® is an extended release formulation it is indicated to be taken twice daily, in the morning and at bedtime. It is available as 0.1-mg and 0.2-mg tablets. The tablets are not scored and should not be crushed or broken. Similar warnings and precautions for clonidine apply. Kapvay® is currently not available on the market.

Xyrem® (sodium oxybate) – is a schedule III medication indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy and was FDA approved in 2002. Xyrem® is an oral solution indicated to be taken at bedtime while in bed and again 2.5 to 4 hours later. The use of Xyrem® has been minimal until recently in 2010. In 2010, Jazz pharmaceuticals also submitted a request for approval for Xyrem® to be used for the treatment of fibromyalgia; however the FDA advisory panel overwhelming rejected the application in August of 2010. All Xyrem® prescriptions are filled by a central, mail order pharmacy via the following process:

1. The physician sends the Xyrem® prescription directly to the pharmacy.
2. A team member from the pharmacy will contact the patient within 48 hours of receiving the prescription to review insurance information.

3. The pharmacy will confirm that the patient has received and/or understood the educational booklet. If the physician did not provide these materials to the patient, the pharmacy will review them with the patient before sending the patient's first shipment of Xyrem®.
4. The pharmacy will always confirm where and when the patient would like Xyrem® delivered and who will sign for the shipment. Xyrem® will be shipped via an overnight courier. When the courier arrives the patient or patient's designated person must sign for the Xyrem® delivery.

The following shows the most recent utilization trends for this medication. There was no utilization of Xyrem® until 2008.

Calendar Year	Members	Claims	Total Cost	Cost/Claim	Perdiem	Units	Days
2008	1	5	$2,677.25	$535.45	$22.31	1,260	120
2009	1	6	$5,213.82	$868.97	$28.97	1,620	180
2010*	5	22	$40,238.38	$1,829.02	$63.57	8,370	633
Percent Change	**400.00%**	**340.00%**	**1,403.00%**	**241.60%**	**184.90%**	**564.30%**	**427.50%**
Change	**4**	**17**	**$37,561.13**	**$1,293.57**	**$41.26**	**7,110**	**513**

***2010 data complete up to the month of November.**

RECOMMENDATIONS

The College recommends the addition of Kapvay® in Tier-2 and Xyrem® in Tier 3 of the ADHD/Narcolepsy PBPA category with a hard edit. In addition the College recommends changes to the current criteria as shown in red.

For Tier 2 Products:

1. FDA approved diagnosis.
2. Trials of long acting medications from both the amphetamine and methylphenidate category, or a non-stimulant medication if a Tier 2 non-stimulant medication is requested, that did not yield adequate response.
   a. Trials should have been within the last 30-60 days.
   b. Dosed up to maximum recommended dose or provide information regarding side effects at higher dose.
   c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician.
3. ~~Clinical exception for non-stimulants if tics or substance abuse is present.~~
4. Concomitant use of stimulants and non-stimulant medication is approved only for members with severe disease who have tried multiple stimulant medications alone, titrated to maximum recommended dose, AND the non-stimulant medication alone, titrated to maximum recommended dose, that did not yield adequate response.
5. ~~An immediate release product of the same drug type may be used concurrently if an afternoon dose is required.~~

For Tier 3 Products:

1. FDA approved diagnosis
2. Trials with at least three lower tiered medications, each from different chemical categories, unless contraindicated, that did not yield adequate response.
   a. Trials should have been within the last 60-90 days.
   b. Dosed up to maximum recommended dose or provide information regarding side effects at higher dose.
   c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician.
4. Concomitant use of stimulants and non-stimulant medication is approved only for members with severe disease who have tried multiple stimulant medications alone, titrated to maximum recommended dose, AND the non-stimulant medication alone, titrated to maximum recommended dose, that did not yield adequate response.
5. ~~All other Tier 2 criteria apply.~~

For all Tiers:

1. Dose exceeding 1.5 times the FDA maximum is not covered.
2. ~~2.~~ Prior Authorization is required for all tiers for members greater than 20 years of age. ~~Must have an FDA approved indication.~~

2011 Tiers based on Net Cost after Supplemental Rebates.

Tier 1	Tier 2	Tier 3
Amphetamine	**Amphetamine**	**Amphetamine**
Adderall®	Vyvanse®	Desoxyn®
Adderall XR®	**Methylphenidate**	Dexedrine®
Methylphenidate	Metadate ER®	Dexedrine Spansules®
Ritalin®	Metadate CD®	ProCentra™ Oral Solution
Methylin®	Ritalin LA®	**Methylphenidate**
Ritalin SR®	**Non-Stimulant**	Daytrana™ Patch
Concerta®	Intuniv®	**Non-Stimulant**
Focalin®	**Kapvay®**	Provigil®
Focalin XR®		Nuvigil®
Non-Stimulant		**Xyrem®**
Strattera®		

Mandatory Generic Plan Applies.
Current Tiers based on Supplemental Rebate Participation

Utilization Details for Fiscal Year 2010

	Medication	Claims	Members	Amount Paid	Units/ Day	Claims/ Day	Paid/ Day	% Paid
Methylphenidate	DAYTRANA DIS 10MG/9HR	315	103	$47,186.21	1.00	3.06	$5.03	0.18%
	DAYTRANA DIS 15MG/9HR	446	112	$69,084.22	1.00	3.98	$5.17	0.27%
	DAYTRANA DIS 20MG/9HR	642	155	$100,970.14	1.04	4.14	$5.25	0.39%
	DAYTRANA DIS 30MG/9HR	845	164	$126,041.03	1.00	5.15	$4.97	0.48%
	METADATE CD CAP 10MG	276	85	$29,584.05	1.00	3.25	$3.61	0.11%
	METADATE CD CAP 20MG	616	158	$71,735.72	1.07	3.90	$3.90	0.28%
	METADATE CD CAP 30MG	684	150	$77,245.17	1.06	4.56	$3.78	0.30%
	METADATE CD CAP 40MG	595	117	$91,873.47	1.04	5.09	$5.18	0.35%
	METADATE CD CAP 50MG	176	37	$31,233.69	0.94	4.76	$5.57	0.12%
	METADATE CD CAP 60MG	287	55	$52,025.51	1.00	5.22	$6.05	0.20%
	METHYLPHENID TAB 5MG	3,112	1,154	$35,395.30	1.72	2.70	$0.39	0.14%
	METHYLIN TAB 5MG	1,876	732	$18,725.22	1.76	2.56	$0.33	0.07%
	METHYLPHENID TAB 10MG	3,824	1,164	$50,040.98	1.81	3.29	$0.44	0.19%
	METHYLIN TAB 10MG	3,480	1,024	$39,207.12	1.83	3.40	$0.38	0.15%
	METHYLPHENID TAB 20MG	1,494	402	$25,648.35	2.05	3.72	$0.57	0.10%
	METHYLIN TAB 20MG	1,225	307	$21,271.97	2.01	3.99	$0.58	0.08%
	RITALIN TAB 20MG	13	2	$1,574.88	2.73	6.50	$4.04	0.01%
	METHYLIN ER TAB 10MG	405	142	$11,961.94	1.23	2.85	$1.00	0.05%
	METHYLIN ER TAB 20MG	1,351	432	$20,749.36	1.25	3.13	$0.50	0.08%
	METHYLPHENID TAB 20MG SR	812	244	$13,458.24	1.33	3.33	$0.51	0.05%
	METADATE TAB 20MG ER	19	7	$281.63	1.08	2.71	$0.46	0.00%
	CONCERTA TAB 18MG	9,035	3,517	$1,187,000.78	1.00	2.57	$4.50	4.57%
	CONCERTA TAB 27MG	9,169	2,717	$1,241,076.87	1.00	3.37	$4.58	4.77%
	CONCERTA TAB 36MG	17,589	3,947	$3,011,881.07	1.24	4.46	$5.75	11.58%
	CONCERTA TAB 54MG	13,090	2,472	$2,001,673.83	1.01	5.30	$5.13	7.70%
	METHYLIN CHW 2.5MG	33	16	$3,018.72	1.91	2.06	$2.96	0.01%
	METHYLIN CHW 5MG	113	35	$11,977.92	1.64	3.23	$3.63	0.05%
	METHYLIN CHW 10MG	49	15	$8,737.70	1.93	3.27	$6.13	0.03%
	METHYLIN SOL 5MG/5ML	175	67	$26,941.04	10.42	2.61	$5.30	0.10%
	METHYLIN SOL 10MG/5ML	203	45	$39,012.16	9.96	4.51	$6.48	0.15%
	RITALIN LA CAP 10MG	222	67	$23,995.00	1.00	3.31	$3.67	0.09%
	RITALIN LA CAP 20MG	445	118	$50,602.68	1.04	3.77	$3.84	0.19%
	RITALIN LA CAP 30MG	666	138	$90,661.03	1.19	4.83	$4.51	0.35%
	RITALIN LA CAP 40MG	636	106	$75,122.51	1.02	6.00	$3.97	0.29%
	Subtotals	**73,918**		**$8,706,995.51**	**1.86**	**3.84**	**$3.48**	**33.48%**
Amphetamine-Dextroamphetamine	AMPHETAMINE TAB 5MG	6,035	1,856	$97,413.42	1.50	3.25	$0.54	0.37%
	AMPHETAMINE TAB 7.5MG	326	92	$6,466.14	1.38	3.54	$0.67	0.02%
	AMPHETAMINE TAB 10MG	7,429	2,022	$133,419.52	1.58	3.67	$0.60	0.51%
	ADDERALL TAB 10MG	2	1	$198.64	1.00	2.00	$3.31	0.00%
	AMPHETAMINE TAB 12.5MG	198	52	$4,893.75	1.75	3.81	$0.85	0.02%
	AMPHETAMINE TAB 15MG	1,895	476	$43,988.92	1.60	3.98	$0.77	0.17%
	AMPHETAMINE TAB 20MG	4,358	1,009	$93,018.50	1.73	4.32	$0.71	0.36%
	AMPHETAMINE TAB 30MG	2,002	411	$61,457.96	1.69	4.87	$1.03	0.24%
	ADDERALL TAB 30MG	7	2	$1,420.16	2.14	3.50	$6.76	0.01%
	AMPHETAMINE CAP 5MG ER	551	218	$86,067.25	1.00	2.53	$5.29	0.33%
	ADDERALL XR CAP 5MG	366	178	$69,879.55	1.00	2.06	$6.41	0.27%
	AMPHETAMINE CAP 10MG ER	3,490	1,020	$521,410.54	1.00	3.42	$5.03	2.01%
	ADDERALL XR CAP 10MG	832	394	$157,200.04	1.00	2.11	$6.36	0.60%
	AMPHETAMINE CAP 15MG ER	3,211	823	$508,451.46	1.00	3.90	$5.32	1.96%
	ADDERALL XR CAP 15MG	864	345	$166,760.53	1.00	2.50	$6.46	0.64%

	Medication	Claims	Members	Amount Paid	Units/ Day	Claims/ Day	Paid/ Day	% Paid
	AMPHETAMINE CAP 20MG ER	6,477	1,499	$1,033,941.84	1.05	4.32	$5.35	3.98%
	ADDERALL XR CAP 20MG	1,191	460	$233,681.87	1.09	2.59	$6.58	0.90%
	AMPHETAMINE CAP 25MG ER	2,076	480	$332,920.86	1.01	4.33	$5.38	1.28%
	ADDERALL XR CAP 25MG	661	241	$127,981.77	1.00	2.74	$6.46	0.49%
	AMPHETAMINE CAP 30MG ER	6,061	1,152	$962,980.14	1.01	5.26	$5.32	3.70%
	ADDERALL XR CAP 30MG	1,425	503	$266,539.84	1.00	2.83	$6.25	1.03%
	Subtotals	**49,457**		**$4,910,092.70**	**1.26**	**3.41**	**$4.07**	**18.89%**
Lisdexamfetami	VYVANSE CAP 20MG	6,548	2,105	$841,045.94	1.00	3.11	$4.35	3.23%
	VYVANSE CAP 30MG	13,282	3,585	$1,713,640.12	1.00	3.70	$4.34	6.59%
	VYVANSE CAP 40MG	7,509	1,991	$970,560.54	1.01	3.77	$4.35	3.73%
	VYVANSE CAP 50MG	9,395	2,140	$1,227,325.62	1.01	4.39	$4.38	4.72%
	VYVANSE CAP 60MG	3,872	849	$501,344.04	1.00	4.56	$4.35	1.93%
	VYVANSE CAP 70MG	6,202	1,052	$808,235.04	1.01	5.90	$4.37	3.11%
	Subtotals	**46,808**		**$6,062,151.30**	**1.01**	**4.24**	**$4.36**	**23.31%**
Dexmethylphenidate	DEXMETHYLPH TAB 2.5MG	673	274	$17,121.11	1.40	2.46	$0.87	0.07%
	FOCALIN TAB 2.5MG	358	153	$12,028.81	1.46	2.34	$1.12	0.05%
	DEXMETHYLPH TAB 5MG	1,401	504	$44,803.36	1.26	2.78	$1.08	0.17%
	FOCALIN TAB 5MG	1,151	421	$45,184.81	1.26	2.73	$1.32	0.17%
	DEXMETHYLPH TAB 10MG	1,122	333	$50,304.73	1.26	3.37	$1.50	0.19%
	FOCALIN TAB 10MG	983	298	$59,812.01	1.38	3.30	$2.05	0.23%
	FOCALIN XR CAP 5MG	3,600	1,453	$453,954.18	1.00	2.48	$4.29	1.75%
	FOCALIN XR CAP 10MG	6,828	2,077	$873,900.60	1.00	3.29	$4.31	3.36%
	FOCALIN XR CAP 15MG	3,886	1,030	$523,990.11	1.03	3.77	$4.53	2.02%
	FOCALIN XR CAP 20MG	5,259	1,115	$703,479.78	1.02	4.72	$4.49	2.71%
	FOCALIN XR CAP 30MG	201	93	$28,755.03	1.01	2.16	$4.83	0.11%
	Subtotals	**25,462**		**$2,813,334.53**	**1.19**	**3.04**	**$2.76**	**10.83%**
Atomoxetine	STRATTERA CAP 10MG	654	230	$95,424.68	1.06	2.84	$5.10	0.37%
	STRATTERA CAP 18MG	1,210	397	$200,829.93	1.16	3.05	$5.70	0.77%
	STRATTERA CAP 25MG	3,072	841	$501,452.47	1.11	3.65	$5.46	1.93%
	STRATTERA CAP 40MG	4,465	1,137	$755,215.98	1.04	3.93	$5.53	2.90%
	STRATTERA CAP 60MG	3,303	733	$533,823.61	1.00	4.51	$5.35	2.05%
	STRATTERA CAP 80MG	1,945	412	$340,631.85	1.01	4.72	$5.76	1.31%
	STRATTERA CAP 100MG	588	113	$108,075.54	1.00	5.20	$5.82	0.42%
	Subtotals	**15,237**		**$2,535,454.06**	**1.05**	**3.99**	**$5.53**	**9.75%**
	INTUNIV TAB 1MG	465	268	$61,725.45	1.01	1.74	$4.89	0.24%
	INTUNIV TAB 2MG	1,164	535	$162,659.54	1.00	2.18	$4.81	0.63%
	INTUNIV TAB 3MG	1,064	423	$150,530.68	1.00	2.52	$4.84	0.58%
	INTUNIV TAB 4MG	417	152	$59,423.65	1.00	2.74	$4.79	0.23%
	Subtotals (guanfacine)	**3,110**		**$434,339.32**	**1.00**	**2.30**	**$4.83**	**1.68%**
	PROVIGIL TAB 100MG	116	25	$29,811.91	1.00	4.64	$8.73	0.11%
	PROVIGIL TAB 200MG	981	150	$420,431.15	1.10	6.54	$14.28	1.62%
	Subtotals (modafinil)	**1,097**		**$450,243.06**	**1.05**	**5.59**	**$11.51**	**1.73%**
Dextroamphetamine	DEXTROAMPHET TAB 5MG	116	32	$1,717.74	1.55	3.63	$0.49	0.01%
	DEXTROAMPHET TAB 10MG	187	35	$4,887.10	2.95	5.34	$0.88	0.02%
	DEXTROAMPHET CAP 5MG ER	36	11	$1,801.22	1.14	3.27	$1.71	0.01%
	DEXTROAMPHET CAP 10MG ER	138	29	$18,450.08	2.67	4.76	$4.52	0.07%
	DEXTROAMPHET CAP 10MG CR	1	1	$30.05	1.00	1.00	$1.00	0.00%
	DEXTROAMPHET CAP 15MG ER	143	30	$18,331.04	2.12	4.77	$4.35	0.07%
	DEXEDRINE CAP 15MG CR	3	1	$867.32	3.00	3.00	$9.64	0.00%
	DEXTROAMPHET CAP 15MG CR	1	1	$37.27	1.00	1.00	$1.24	0.00%
	Subtotals	**625**		**$46,121.82**	**2.33**	**3.35**	**$2.98**	**0.18%**

	Medication	Claims	Members	Amount Paid	Units/ Day	Claims/ Day	Paid/ Day	% Paid
	NUVIGIL TAB 150MG	80	26	$23,060.30	1.01	3.08	$9.80	0.09%
	NUVIGIL TAB 250MG	39	11	$12,354.74	1.10	3.55	$10.62	0.05%
	Subtotals (armodafinil)	**119**		**$35,415.04**	**1.06**	**3.32**	**$10.21**	**0.14%**
	DESOXYN TAB 5MG	13	1	$7,174.60	5.00	13.00	$18.40	0.03%
	Subtotals (methamphetamine)	**13**		**$7,174.60**	**5.00**	**13.00**	**$18.40**	**0.03%**
	Total	**215,846**	**29,425***	**$26,001,321.94**	**1.18**	**7.34**	**$4.05**	**100%**

***Total number of unduplicated members.**

Product Details of Kapvay® (clonidine extended release) Oral Tablets[7]

Shionogi Pharma, Inc.

INDICATIONS: Kapvay® is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications.

DOSAGE FORMS: Extended-release tablets: 0.1mg and 0.2mg; tablets are not scored.

DOSING & ADMINISTRATION:

- Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved.
- Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime. While it is dosed twice a day, the same as the immediate-release clonidine formulation, it is not to be used interchangeably with the immediate-release formulation.
- Kapvay ® is an extended-release tablet and, therefore, must be swallowed whole and never crushed, cut or chewed.
- While it is dosed twice a day, the same as the immediate-release clonidine formulation, it is not to be used interchangeably with the immediate-release formulation. Do not substitute for other clonidine products on a mg-per-mg basis, because of differing pharmacokinetic profiles.
- When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days.
- Kapvay ® may be taken with or without food.

CONTRAINDICATIONS: Kapvay® should not be used in patients with known hypersensitivity to clonidine.

SPECIAL POPULATIONS:

- Pregnancy Category C
- Since clonidine hydrochloride is excreted in human milk, caution should be exercised when Kapvay® is administered to a nursing woman.
- Kapvay® has not been studied in children less than 6 years old.
- Renal Insufficiency: The dosage of Kapvay® must be adjusted according to the degree of impairment, and patients should be carefully monitored.

WARNINGS & PRECAUTIONS:

- **Hypotension/bradycardia**: Use Kapvay® with caution in patients at risk for hypotension, bradycardia, and heart block. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated.
- **Somnolence/Sedation:** Has been observed with Kapvay®. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to Kapvay®.
- **Abrupt Discontinuation**: Patients should be instructed not to discontinue Kapvay® therapy without consulting their physician due to the potential risk of withdrawal effects. Kapvay® should be discontinued slowly in decrements of no more than 0.1 mg every 3 to 7 days. (5.3)
- **Use in patients with vascular disease, cardiac conduction disease, or chronic renal failure**: Monitor carefully and uptitrate slowly. (5.5)
- **Other clonidine containing products**: Do not use Kapvay ® concomitantly with other products containing clonidine, (e.g. Catapres®)
- **Allergic Reactions**: In patients who have developed localized contact sensitization or other allergic reaction to clonidine in a transdermal system, substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash, urticaria, or angioedema.

ADVERSE REACTIONS (incidence at least 5% and twice the rate of placebo)

- somnolence

- fatigue
- upper respiratory tract infection (cough, rhinitis, sneezing)
- irritability
- throat pain (sore throat)
- insomnia
- nightmares
- emotional disorder
- constipation,
- nasal congestion
- increased body temperature
- dry mouth
- ear pain

DRUG INTERACTIONS:

- Sedating Drugs: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs.
- Tricyclic Antidepressants: May reduce the hypotensive effect of clonidine.
- Drugs Known to Affect Sinus Node Function or AV Nodal Conduction: Caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers) due to a potential for additive effects such as bradycardia and AV block.
- Use with other products containing clonidine: Do not use Kapvay® concomitantly with other products containing clonidine (e.g. Catapres®
- Antihypertensive drugs: Use caution when coadministered with Kapvay®.

INFORMATION FOR PATIENTS

- Kapvay® should be taken 2 times a day (in the morning and at bedtime).
- If you miss a dose of Kapvay®, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time.
- Take Kapvay® tablets whole. Do not chew, crush or break Kapvay® tablets. Tell your doctor if you cannot swallow Kapvay® tablets whole. You may need a different medicine.
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking Kapvay® until you talk with your doctor. Kapvay® taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery or do other dangerous activities until you know how Kapvay® will affect you.
- Avoid becoming dehydrated or overheated.
- Suddenly stopping Kapvay® may cause withdrawal symptoms including: increased blood pressure, headache, increased heart rate, lightheadedness, tightness in your chest and nervousness.

Product Details of Xyrem® (sodium oxybate) Oral Solution[8]

Jazz Pharmaceuticals, Inc.

INDICATIONS: Xyrem® (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

DOSAGE FORMS: supplied in 180 mL bottles (500 mg/mL) of Xyrem®, one press-in-bottle-adaptor and one oral dispensing syringe.

DOSING & ADMINISTRATION:

- Xyrem® is required to be taken at bedtime while in bed and again 2.5 to 4 hours later.
- The dose of Xyrem® should be titrated to effect.
- The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose).
- One to two weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects.
- The effective dose range of Xyrem® is 6 to 9 g/night.
- The efficacy and safety of Xyrem® at doses higher than 9 g/night have not been investigated, and doses greater than 9 g/night ordinarily should not be administered.

CONTRAINDICATIONS:

- Sodium oxybate is contraindicated in patients being treated with sedative hypnotic agents.
- Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism variably characterized by mental retardation, hypotonia,and ataxia.

SPECIAL POPULATIONS:

- Pregnancy Category B
- The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.
- Pediatric-The pharmacokinetics of sodium oxybate in patients under the age of 18 years have not been studied.
- Gender-In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 g.
- Race-There are insufficient data to evaluate any pharmacokinetic differences among races.
- Renal Disease-Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium
- oxybate pharmacokinetics would be expected.
- Hepatic Disease-Sodium oxybate undergoes significant first-pass metabolism. It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction

WARNINGS & PRECAUTIONS:

- **potential for abuse**; linked with serious CNS effects, including seizure, respiratory depression, and death
- **do not use with alcohol or other CNS depressants**; potentiation of CNS depressant effects of sodium oxybate
- **cardiac failure**; due to sodium content of drug
- **compromised liver function**; increased elimination half-life and systemic exposure to sodium oxybate
- **compromised renal function**; due to sodium content of drug
- **compromised respiratory function**; risk of developing sleep apnea and respiratory depression
- **hypertension**; due to sodium content of drug
- **previous history of depressive illness/suicide**; risk of
- **should be taken only at bedtime, and while in bed**; rapid onset of CNS depressant effects
- **sleep apnea**; high incidence (up to 50%) reported in cohorts of narcoleptic patients
- **Confusion/Neuropsychiatric Adverse Events -** During clinical trials, 2.6% of patients treated with sodium oxybate experienced confusion. Other neuropsychiatric events included psychosis, paranoia, hallucinations,

and agitation. The emergence of thought disorders and/or behavior abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

- **Depression -** In clinical trials, 3.2% of patients treated with sodium oxybate reported depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required.
- **Incontinence -** During clinical trials, 7% of narcoleptic patients treated with sodium oxybate experienced either a single episode or sporadic nocturnal urinary incontinence and <1% experienced a single episode of nocturnal fecal incontinence.
- **Sleepwalking -** The term "sleepwalking" in this section refers to confused behavior occurring at night and, at times, associated with wandering. Sleepwalking was reported in 4% of 717 patients treated in clinical trials with sodium oxybate. Sleepwalking was reported by 32% of patients treated with sodium oxybate for periods up to 16 years in one independent uncontrolled trial.
- **Withdrawal effects**: Effects are similar to other sedative-hypnotic withdrawal syndromes and may develop following abrupt abstinence after frequent, chronic use.

Xyrem® has the following Black Box warning:

!WARNING: Central nervous system depressant with abuse potential.

Should not be used with alcohol or other CNS depressants. Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants. Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).

Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1-866-XYREM88® (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer.

DRUG INTERACTIONS: Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics.

INFORMATION FOR PATIENTS

- Prepare both doses of Xyrem® prior to bedtime. Each dose of Xyrem® must be diluted with two ounces (60 mL, 1/4 cup, or 4 tablespoons) of water in the child-resistant dosing cups provided prior to ingestion.
- The first dose is to be taken at bedtime and the second taken 2.5 to 4 hours later; both doses should be taken while seated in bed. Patients will probably need to set an alarm to awaken for the second dose.
- The second dose must be prepared prior to ingesting the first dose, and should be placed in close proximity to the patient's bed. After ingesting each dose patients should then lie down and remain in bed.
- Patients should also be informed that they should be seen by the prescriber frequently during the course of their treatment to review dose titration, symptom response and adverse reactions.
- Food significantly decreases the bioavailability of sodium oxybate (see Pharmacokinetics). Whether sodium oxybate is taken in the fed or fasted state may affect both the efficacy and safety of sodium oxybate for a given patient. Patients should be made aware of this and try to take the first dose several hours after a meal.
- Patients should be informed that sodium oxybate is associated with urinary and, less frequently, fecal incontinence. Patients should be instructed that they should not take alcohol or other sedative hypnotics with sodium oxybate.

References

[1] http://www.jnj.com/connect/news/all/concerta-patent-appeal-denied
[2] http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
[3] http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
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[7] **Kapvay®® Label Information. Shionogi Pharma, Inc**. Available online at http://Kapvay®.com/Kapvay® final 09.28.10.pdf. Last revised September 2010.
[8] **Xyrem® Label Information. Jazz Pharmaceuticals, Inc**. Available online at http://www.xyrem.com/xyrem-pi.pdf

Appendix I

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Safety

Avastin (bevacizumab): Process for Removal of Breast Cancer Indication Begun

[Posted 12/16/2010]

AUDIENCE: Oncology, Patients

ISSUE: FDA notified healthcare professionals and patients that it is recommending removing the breast cancer indication for Avastin (bevacizumab) because the drug has not been shown to be safe and effective for that use. The drug itself is not being removed from the market and today's action will not have any immediate impact on its use in treating breast cancer. Today's action will not affect the approvals for colon, kidney, brain, and lung cancers.

BACKGROUND: FDA is making this recommendation after reviewing the results of four clinical studies of Avastin in women with breast cancer and determining that the data indicate that the drug does not prolong overall survival in breast cancer patients or provide a sufficient benefit in slowing disease progression to outweigh the significant risk to patients. None of the studies demonstrated that patients receiving Avastin lived longer and patients receiving Avastin experienced a significant increase in serious side effects. These risks include severe high blood pressure; bleeding and hemorrhage; the development of perforations (or "holes") in the body, including in the nose, stomach, and intestines; and heart attack or heart failure.

RECOMMENDATION: Oncologists currently treating patients with Avastin for metastatic breast cancer should use their medical judgment when deciding whether a patient should continue treatment with the drug or consider other therapeutic options.

Patients currently receiving Avastin for breast cancer should speak with their oncologists about whether to continue their treatment or explore other treatment options.

[12/16/2010 - News Release[1] - FDA]
[12/16/2010 - Questions and Answers about Avastin[2] - FDA]
[12/15/2010 - Avastin Decision Memo (PDF - 125KB)[3] - FDA]

Links on this page:

1. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm237172.htm
2. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm237095.htm
3. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237171.pdf

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Ongoing safety review of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death

Safety Announcement

[12-22-2010] The U.S. Food and Drug Administration (FDA) is informing the public that results from a study conducted in France—the Santé Adulte GH Enfant (SAGhE) study—found that persons with certain kinds of short stature (idiopathic growth hormone deficiency and idiopathic or gestational short stature) treated with recombinant human growth hormone during childhood and who were followed over a long period of time, were at a small increased risk of death when compared to individuals in the general population of France. FDA is currently reviewing all available information on this potential risk and will communicate any new recommendations once it has completed its review.

At this time, FDA recommends that patients continue their recombinant human growth hormone treatment as prescribed by their healthcare provider.

Recombinant human growth hormone is a protein that is manufactured to be nearly identical to the main form of the naturally occurring human growth hormone. This hormone can stimulate tissue growth, linear growth (height), and protein, carbohydrate, lipid, and mineral metabolism. It has approved indications in both the adult and pediatric populations. In the United States, recombinant human growth hormone is used in the pediatric population to treat short stature due to growth hormone deficiency (including idiopathic [of unknown cause] growth hormone deficiency), Turner syndrome, Noonan syndrome, Prader-Willi syndrome, short stature homeobox-containing gene (SHOX) deficiency, chronic renal insufficiency, idiopathic short stature and children small for gestational age.

The SAGhE study is reported to be a long-term epidemiological study.[1-3] It was designed to assess the long-term mortality of patients treated with recombinant human growth hormone during childhood. The study population was based on a mandatory registry of patients in France who received recombinant human growth hormone treatment during childhood between 1985 and 1996 and whose vital status and cause of death was determined through September 2009.

Recombinant human growth hormone, also known as somatropin [rDNA origin] injection, is marketed under the following brand names in the United States: Genotropin, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, and Tev-Tropin.

(see Data Summary below)

Additional Information for Patients and Caregivers

- Do not stop taking recombinant human growth hormone without talking to your healthcare professional.
- Discuss any questions or concerns about recombinant human growth hormone with your healthcare professional.
- Report any side effects you experience to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- At this time, FDA believes the benefits of recombinant growth hormone continue to outweigh its potential risks.
- If you prescribe recombinant human growth hormone, follow the recommended indications and doses in the product labels.
- Report adverse events involving recombinant human growth hormone to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page

Data Summary

FDA is aware of the results of a long-term epidemiological study called SAGhE (Santé Adulte GH Enfant), which was designed to assess the long-term mortality of patients treated with recombinant human growth hormone during childhood.[1-3] This study was based on a mandatory registry of patients in France treated with recombinant growth hormone during childhood between 1985 and 1996.

The investigators report a 30% increased risk of death with recombinant human growth hormone therapy compared to the general population, with 93 observed deaths in the treated group versus 70 expected deaths in the general population in France. The data suggest an increase in mortality due to bone tumors and cardiovascular diseases includin cerebrovascular events (mainly subarachnoid or intracerebral hemorrhage).

The risk of death was reported to be increased when doses of recombinant growth hormone that are higher than what is normally prescribed for pediatric growth hormone deficiency were used. The approved doses in the United States for pediatric growth hormone deficiency are below 50 mcg/kg/day, except during puberty, when a higher dose regimen is approved for a limited duration of time.For short stature indications other than growth hormone deficiency, doses up to 69 mcg/kg/day (0.48 mg/kg/week) are currently approved.

In summary, the SAGhE study reported an increased risk of death in patients who were treated with recombinant huma growth hormone during childhood when compared to individuals in the general population of France. FDA is currently reviewing all available new information on this potential risk and at this time, recommends caution when interpreting th reported results. Additionally, FDA believes the benefits of recombinant growth hormone continue to outweigh the potential risks. Patients should continue to follow the advice of their healthcare provider. FDA will communicate with the public as soon as we have completed our evaluation. Further information is available in the European Medicines Agency (EMA) press releases[1,3] and the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) press release (in French).[2]

1. European Medicines Agency to review the safety of somatropin-containing medicines. December 10, 2010[1] (press release). Accessed on December 13, 2010
2. Recombinant growth hormone (recombinant somatropin); first results of the long-term epidemiological study SAGhE. Agence Francaise de Securite Sanitaire des Produits de Sante, December 10, 2010[2] (press release). Accessed on December 13, 2010.
3. European Medicines Agency. Update on somatropin-containing medicines; Review of somatropin officially started. December 16, 2010[3] (press release). Accessed on December 18, 2010.

Related Information

- European Medicines Agency to review the safety of somatropin-containing medicines. December 10, 2010[4] [5]
- Recombinant growth hormone (recombinant somatropin); first results of the long-term epidemiological study SAGhE. Agence Francaise de Securite Sanitaire des Produits de Sante, December 10, 2010[6] [7]
- European Medicines Agency. Update on somatropin-containing medicines; Review of somatropin officially started. December 16, 2010[8] [9]
- Somatropin Information[10]

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Links on this page:

1. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/12/news_detail_001160.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Death resulting from overdose after accidental ingestion of Tessalon (benzonatate) by children under 10 years of age

Safety Announcement

[12-14-2010] The U.S. Food and Drug Administration (FDA) is warning the public that accidental ingestion of benzonatate by children under the age of 10 years can result in death from overdose.

Benzonatate is a prescription drug approved for relief of cough in patients over 10 years of age. The safety and effectiveness of benzonatate in children under 10 years of age have not been established. Benzonatate is sold under the brand-name Tessalon and is also sold in generic preparations.

Benzonatate may be attractive to children because of the drug's appearance (it is a round-shaped liquid-filled gelatin capsule).

Image reprinted with permission from Medscape.com, 2010.

Image reprinted with permission from Medscape.com, 2010.

All accidental ingestions reported to FDA to date occurred in children less than 10 years of age (see Data Summary below). Overdose with benzonatate in children less than 2 years of age has been reported following accidenta ingestion of as few as 1 or 2 capsules. Individuals who experience overdose of benzonatate may exhibit restlessness, tremors, convulsions, coma, and cardiac arrest. Signs and symptoms of overdose can occur rapidly after ingestion (within 15-20 minutes). Deaths in children have been reported within hours of the accidental ingestion.

Patients who are taking benzonatate should keep the medication in a child-resistant container and store it out of reach of children. If a child accidentally ingests benzonatate, seek medical attention immediately.

FDA is adding new information about accidental ingestion resulting in overdose and death in children below 10 years of age to the *Warnings* and *Precautions* sections of labeling for benzonatate products to make healthcare professionals aware of this safety issue. FDA encourages healthcare professionals to talk with their patients about this risk.

Additional Information for Patients and Caregivers

- Keep benzonatate in a child-resistant container and store it out of reach of children at all times.
- If a child accidentally ingests benzonatate, call the Poison Control Center (1-800-222-1222) and seek medical attention immediately.
- Signs and symptoms of benzonatate overdose can occur rapidly after ingestion (within 15-20 minutes) and may

include restlessness, tremors, convulsions, coma, and cardiac arrest.

- Benzonatate capsules are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. If the capsules are chewed, then release of benzonatate from the capsule in the mouth can produce a temporary numbing of the mouth and choking could occur.
- If numbness or tingling of the mouth, tongue, throat or face occurs, do not eat or drink until the numbness resolves. If the symptoms worsen or persist, seek medical attention.
- Overdose of benzonatate has been reported in adults and adolescents. If you miss a dose of benzonatate, skip tha dose and take the next dose at the next scheduled time.
- Do not take more than 200 mg of benzonatate at one time.
- Patients and caregivers should dispose of any leftover benzonatate in their household trash (see Federal Drug Disposal Guidelines[1]):
  - Take the medication out of its original container and mix it with an undesirable substance, such as used coffee grounds or kitty litter. The medication will be less appealing to children and pets, and unrecognizable to people who may intentionally go through your trash.
  - Put the medication in a sealable bag, empty can with a tight lid, or other container to prevent it from breaking out of a garbage bag.
- Report any side effects or medication errors from the use of benzonatate to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Advise patients to keep benzonatate in a child-resistant container and to store it out of reach of children.
- Counsel patients about how to properly dispose of leftover benzonatate after they have stopped taking the medication (see Federal Drug Disposal Guidelines[2]).
- Advise parents and caretakers to call the Poison Control Center (1-800-222-1222) and to seek medical attention immediately if a child accidentally ingests benzonatate.
- Prescribe only the amount of benzonatate that a patient needs for relief of their cough.
- Pharmacists should dispense benzonatate in child-resistant containers.
- Recognize the signs and symptoms of benzonatate overdose, which may include restlessness, tremors, convulsions, coma, and cardiac arrest.
- Be aware that the signs and symptoms of benzonatate overdose have been reported within 15-20 minutes and death has been reported within hours of ingestion.
- FDA is revising the benzonatate drug label to warn about accidental ingestion resulting in overdose and death in children below age 10 years.
- The safety and effectiveness of benzonatate in children below the age of 10 years have not been established. Therefore, prescribing benzonatate to that age group is not recommended.
- Advise patients to swallow benzonatate capsules whole and to not break, chew, dissolve, or crush the capsules. Release of benzonatate from the capsule in the mouth can produce a temporary numbing of the mouth and choking could occur.
- Overdose of benzonatate has been reported in adults and adolescents. Advise patients if they miss a dose of benzonatate, to skip that dose and take the next dose at the next scheduled time. They should not take 2 doses of benzonatate at one time. A single dose of benzonatate should not exceed 200 mg and the total daily dosage shoul not exceed 600 mg.
- Report adverse events and medication errors involving benzonatate to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

Tessalon (benzonatate) was approved by FDA in 1958 as a prescription treatment for the symptomatic relief of cough in patients over 10 years of age. Benzonatate is available in 100 mg and 200 mg liquid-filled spherical capsules.

A search of FDA's Adverse Event Reporting System (AERS) database through May 19, 2010 identified 31 cases of overdose associated with benzonatate (median age 18 years, range 1 to 66 years). Common adverse events reported ir the overdose cases included cardiac arrest, coma, and convulsion. The quantities ingested ranged from 1 or 2 to 30 benzonatate capsules. Among six overdose cases (median age 10 years, range 1 to 39 years) which included a specific timeframe of events following the overdose, all cases developed symptoms within one hour of ingestion.

Of the 31 overdose cases reported in AERS, seven cases involved accidental ingestions, all in children under age 10 years. Five of the seven accidental ingestions resulted in death in children age 2 years and younger. Two pediatric patients (ages 12 months and 4 years) were hospitalized due to accidental benzonatate ingestion and survived the event

Related Information

- FDA says Tessalon liquid cough capsules pose risk for young children[3]
  FDA news release (12/14/2010)
- How to Dispose of Unused Medicines[4]
  FDA Consumer Update
- Tessalon (benzonatate) Information[5]

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2. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm101653.htm
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6. http://www.fda.govhttps://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
7. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

About FDA

Drug Safety Oversight Board Meeting, November 18, 2010

Public Summary

The Executive Director updated the Drug Safety Oversight Board (DSB or Board) on Drug Safety Communications poste and in development since the October 21, 2010 meeting. The following is a list of the posted risk communications:

Drug Safety Communications Posted since the October 21, 2010 DSB meeting:

- October 21, 2010: Invirase (saquinavir) labels now contain updated risk information on abnormal heart rhythms[1]: FDA issued a DSC notifying the public that new risk information has been added to the label of the antiviral drug Invirase (saquinavir), describing a potential change in the electrical activity of the heart when Invirase is used wit another antiviral medication, Norvir (ritonavir). The PR or QT interval can be prolonged, leading to potential arrhythmias.

The DSB discussed three topics:
1. Update on Tablet Splitting/Scoring
2. Benzocaine and Methemoglobinemia
3. A draft Drug Safety Communication (DSC) related to a prescription product used to treat cough

The views expressed by non-CDER employees are those of the individual and not necessarily the opinion of their respective government agency.

Update on Tablet Splitting/Scoring

Tablet splitting refers to cutting a tablet, usually in half, so as to provide flexibility in dosing of a drug or as a cost-savinç measure. For example, some drugs are monitored with blood tests that allow the dosage to be adjusted to achieve a therapeutic goal. In addition, in some instances, a tablet with double the amount of drug costs less than double the price of two smaller tablets. In this instance, cutting the tablet in half can save on medication cost. Tablets often have a line o "score" in the tablet to facilitate splitting but often the tablets do not split into equal segments. A tablet splitting tool can be used as an aid but also does not ensure uniform segments on splitting.

The Board invited a guest expert from the US Pharmacopoeia (USP), Dr. Anthony DeStefano, Vice President of the General Chapters at the USP. Dr. DeStefano spoke about the history of the USP and its current collaboration with FDA o the tablet scoring and splitting issue.

The Board discussed the following:

- An overview of the practice of tablet splitting and tablet scoring
- Progress on a draft guidance regarding tablet scoring
- Perspectives about tablet scoring from the US Pharmacopoeia Input from the federal partners on the DSB regarding their experience with tablet splitting in patient care settings

Benzocaine and Methemoglobinemia

Methemoglobinemia a disorder characterized by the presence of a higher than normal level of methemoglobin (metHgb) in the blood. MetHgb cannot carry oxygen and hinders the unloading of oxygen to tissues. Methemoglobinemia can be congenital or acquired (e.g. induced by drugs or chemicals). FDA has received reports of drug-induced methemoglobinemia associated with benzocaine products used for topical anesthesia.

The Board discussed the following:

- An overview of the safety issue with benzocaine products used for topical anesthesia.
- Previous actions to address this issue
- MedWatch reports received by FDA regarding benzocaine products used for topical anesthesia.
- Scope of the current safety issue
- Possible actions to help address the safety issue

Draft Drug Safety Communication

The Board discussed a draft DSC involving a prescription product approved for the symptomatic treatment of cough in patients over 10 years of age. The product has been rarely associated with death following accidental ingestion by children under 10 years of age. The Board evaluated whether the draft DSC effectively communicated, without alarm, the important messages to consumers and healthcare professionals about proper use of the product, keeping it away

from children, and disposing of leftover medication.

Links on this page:

1. http://www.fda.gov/Drugs/DrugSafety/ucm230096.htm