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Drug Use Evaluation: Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Summary

- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) were primarily developed as antidepressants. Their use for pain conditions has increased, sometimes without strong evidence of effectiveness.
- The Oregon FFS program spent $3 million quarterly on SNRIs in Q3 2010
- While the class utilization and cost has remained relatively flat over the last 15 months, duloxetine costs have risen 7% annually and are associated with 62% of the class costs.
- From July 1, 2009 to September 30, 2010 11,208 unique patients used an SNRI and 57% used one drug for at least 90 continuous days (chronic users)
- 58% of chronic users were on duloxetine and 41% were on venlafaxine.
- More than 2% of chronic users were < 18 years old.
- Diagnostic data suggest that >30% were being treated for depression or anxiety disorders.
- Almost 6% of chronic users were associated with diabetic neuropathy, post herpetic neuropathy or other neuropathies.
- Nearly 87% of milnacipran chronic users, 22% of duloxetine chronic users, 11% of venlafaxine chronic users and 10% of desvenlafaxine chronic users are associated with fibromyalgia (not covered by OHP)
- Only 0.5% of chronic users were on duplicate therapy and 2% exceeded maximum recommended doses.

Drug Use Evaluation: Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a type of antidepressant medication that increases the levels of both serotonin and norepinephrine by inhibiting their reabsorption (reuptake) into cells in the brain. Although the precise mechanism of action isn't clear, it's thought that these higher levels improve and elevate mood. Milnacipran was originally developed and manufactured (in 1997) in France as an antidepressant but is FDA approved for fibromyalgia only. SNRIs are sometimes used to treat anxiety disorders, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), chronic neuropathic pain, fibromyalgia, and for the relief of menopausal symptoms. This review will focus on the use of SNRIs for fibromyalgia and chronic neuropathic pain.

Peripheral Neuropathy (NP)

Neuropathic pain is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching or shooting. Up to 3% of the general population reports NP at some time. NP is most commonly associated with painful diabetic neuropathy, peripheral herpetic neuropathy (PHN) or lumbar nerve root compression. Other causes of NP include cancer-related pain, spinal cord injury, post-stroke pain, HIV-associated neuropathy, phantom limb pain and trigeminal neuralgia. Four drugs are FDA approved for treatment of diabetic neuropathy or PHN: gabapentin, pregabalin, duloxetine and lidocaine patch. A variety of pharmacologic agents from different therapeutic classes have been used for NP treatment. Even so, only 40-60% of patients obtain even partial pain relief for NP with existing pharmacologic agents.(9) Methodology, small sample sizes, short duration studies, lack of head to head trials, and variability in drug classes for treatment of different types of NP limit comparative analysis of many medications.

In a summary of six systematic reviews including a total of 17 unique placebo-controlled trials of gabapentin, 5 trials of pregabalin, 3 trials of venlafaxine, 6 trials of topical lidocaine and 2 trials of duloxetine, there were no published reports of a head-to-head trials of one of these drugs versus another. Adjusted indirect analyses of placebo-controlled trials found gabapentin, duloxetine, and venlafaxine similarly effective for pain relief and improvement in function compared to one another. Pregabalin was moderately superior to duloxetine for the proportion of patients experiencing significant pain relief, but there were no differences between pregabalin and gabapentin or venlafaxine.

Fibromyalgia

Fibromyalgia is characterized by chronic widespread pain and is often associated with other symptoms such as fatigue, sleep disturbance, stiffness, cognitive impairment, and depressed mood. Evidence indicates that the pain associated with fibromyalgia involves a dysfunction in pain and sensory processing systems. It has been hypothesized that abnormal pain processing is an important factor in the dysfunction of descending neuronal pathways in which norepinephrine and serotonin are key

neurotransmitters. These two key neurotransmitters are implicated in enhancing endogenous analgesic mechanisms via the descending nociceptive modulatory pathways in the brain and spinal cord.

Five types of medications are effective in fibromyalgia: (1) TCAs; (2) cyclobenzaprine; (3) tramadol; (4) SNRIs (duloxetine, milnacipran); and (5) α2δ-ligand anticonvulsants (pregabalin, gabapentin). Most research on pharmacotherapy for fibromyalgia over the past 5 years has involved the SNRI antidepressants and the α2δ-ligand anticonvulsants. Pregabalin, duloxetine and milnacipran have each proven effective in several positive Phase III RCTs, and are the first FDA-approved drugs for the treatment of fibromyalgia. Although these are the only FDA approved pharmacologic therapies, TCAs, SSRI/SNRIs, analgesics and anti-anxiety medications have shown efficacy in clinical trials and are often used in therapy. A 2008 systematic review of antidepressants, including milnacipran, in the treatment of fibromyalgia found no evidence of superiority of one class of antidepressant over another.(8) Gabapentin, another α2δ-ligand, was studied in a single trial, which was positive. Another SNRI, venlafaxine, was tested in a low-dose trial (75 mg) and did not differ from placebo. The EULAR (European League Against Rheumatism) and American Pain Society (APS) management of fibromyalgia guidelines indicate effective therapy is a combination of education, pharmacologic and non-pharmacologic treatments.(6,7) EULAR guidelines recommend use of amitriptyline, fluoxetine, duloxetine, milnacipran, pregabalin or tramadol (level of evidence Ib), in combination with non-pharmacologic therapy to reduce pain. Data does not currently support combined use of approved medications in the treatment of fibromyalgia.

Table 1 – Summary of SNRI indications, dosing and cautions

SNRI	FDA Indications		Dosing	Restricted Populations (Cautions and Contraindications)
	Pain	Other		
Duloxetine *(Cymbalta)*	Fibromyalgia DPN Chronic OAP Chronic LBP	MDD GAD	60mg QD* (F) 60-90mg QD (DPN) Max dose = 120mg/d	• Uncontrolled narrow angle glaucoma • Substantial alcohol abuse/chronic liver disease • Severe renal impairment • Hepatotoxicity • Uncontrolled hypertension • Hyponatremia • Increased suicidality in children, adolescents, and young adults with major depressive disorder and other psychiatric conditions. • Drug Interactions: (1) Risk of serotonin syndrome when SNRIs and triptans are used together, (2) concomitant use with MAOIs, (3) concomitant use of phenothiazines • Special populations: Not studied in children (not recommended); no specific recommendation for geriatric patients
Venlafaxine *(Effexor, Effexor XR)*	No	MDD GAD SAD Panic	75mg/d (F), (DPN) Max dose = 375mg/d	• Studies demonstrate high withdrawal rate d/t adverse effects • Similar to duloxetine, less concern about hepatic impairment • Special populations: Not studied in children or elderly for pain indications
Desvenlafaxine *(Pristiq)*	No	MDD	Not studied Max dose = 100mg/d	• Similar to duloxetine, less concern about hepatic impairment • Special populations: Not studied in children or elderly for pain indications
Milnacipran (*Savella*)	Fibromyalgia	None	50mg BID (F) Max dose = 200mg/d	• Similar to duloxetine • Special populations: Not studied in children (not recommended); renal function and risk of hyponatremia need to be considered in elderly

MDD=Major depressive disorder, GAD=Generalized anxiety disorder, DPN=Diabetic peripheral neuropathy, SAD=Social Anxiety disorder,
OAP=Osteoarthritic pain, LBP=Lower back pain, F=Fibromyalgia
*Doses exceeding 60mgQD are not associated with additional clinical improvement

Methods

Trend analysis

A SNRI was defined as duloxetine, venlafaxine, desvenlfaxin and milnacipran . See Appendix A for list of Generic Sequence Numbers used to identify these drugs. Paid, clean, fee-for-service pharmacy claims from July 1, 2009 thru September 30, 2010 were queried for trends in SNRI costs and utilization and quantified as a monthly per member per month (PMPM) value. Costs were defined as ingredient cost (paid amount + copay amount + other insurance paid – dispensing fee) and utilization was defined as the claim count. Total eligibility figures for BMH (OHP Plus) and KIT (OHP standard) benefit packages were used for the denominator. Finally, total and average costs for 30 days were quantified during the third quarter of 2010 for all eligible patients.

SNRI User Analysis

For time period (7/1/09 – 9/10/2010), SNRI users were identified if a single claim was paid. Each SNRI user with at least 90 continuous days of therapy was included in the chronic use cohort. Continuous therapy is defined as sequential claims where the beginning of the next claim is no greater than 14 days after the end of the previous claim. The "end" of a claim is defined as claim date + day supply. Demographic information such as age, sex, and race were quantified in all SNRI users as well as the chronic use cohort.

From the chronic use cohort the prevalence of patients on more than one SNRI was characterized. Duplicate SNRI use was defined as being prescribed two unique SNRI with a continuous overlap of at least 90 days. The average dose and number of subjects exceeding the maximum dose was also described.

Among all users, chronic users, and duplicate users we characterized the prevalence of diagnoses that may be common for SNRI users. Specifically, we used ICD9CM codes from paid, clean, FFS or FCHP medical claims submitted from 7/1/2008- 9/30/10 to quantify the number of patients with a number of conditions known to be treated with SNRIs. See Table 2 for definitions.

Table 2: Diagnoses Definitions

Diagnosis Group	ICD9
Depressive disorder NOS	311xx
Major Depressive Disorder	2962x. 2963x,
Diabetes with neurological manifestations	2506x
Herpes zoster with nervous system complications	0531x
Anxiety disorders	300xx
Fibromyalgia	7291x

Finally, we quantified which prescriptions were associated with prescribers with a psychiatry, pain or primary care background. Specialty definitions were drawn from provider enrollment information summarized in Table 3.

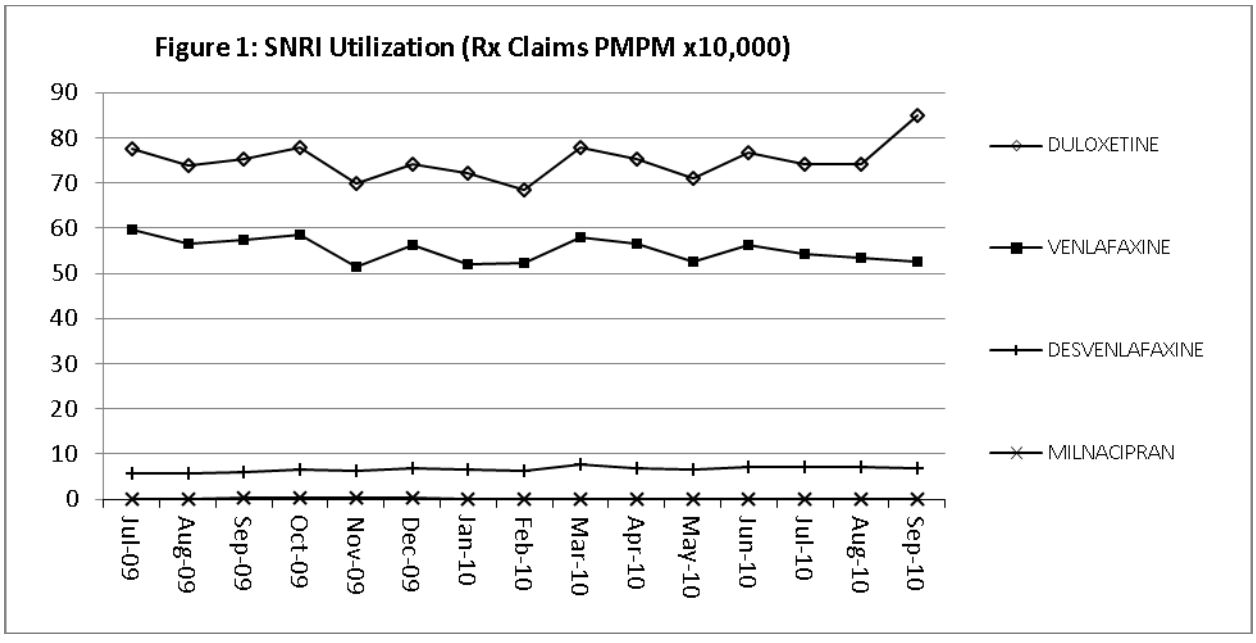
Table 3 – Precriber Specialty Definitions

Psychiatry	
227	Psychiatrist
312	Psychiatrist
365	Psychiatric Mental Health Nurse Practitioner
Pain	
278	Oncologist
228	Anesthesiologist
236	Child Neurology
266	Neuropathology
268	Neurologist
291	Physical Medicine and Rehabilitation Practitioner
299	Rheumatology
Primary Care	
249	Family Practitioner
262	Internist
283	Pediatrics
364	Family Nurse Practitioner

Results

Trend Analyses

From July 2009 to September 2010 utilization of SNRIs has remained relatively flat with only duloxetine increasing. It increased in cost 7% from Q3 2009 to Q3 2010 and accounts for 62% of SNRI costs. Figures 1 and 2 display the utilization and cost changes PMPM occurring for each SNRI during this period. Table 4 summarizes Q3 2010 costs.



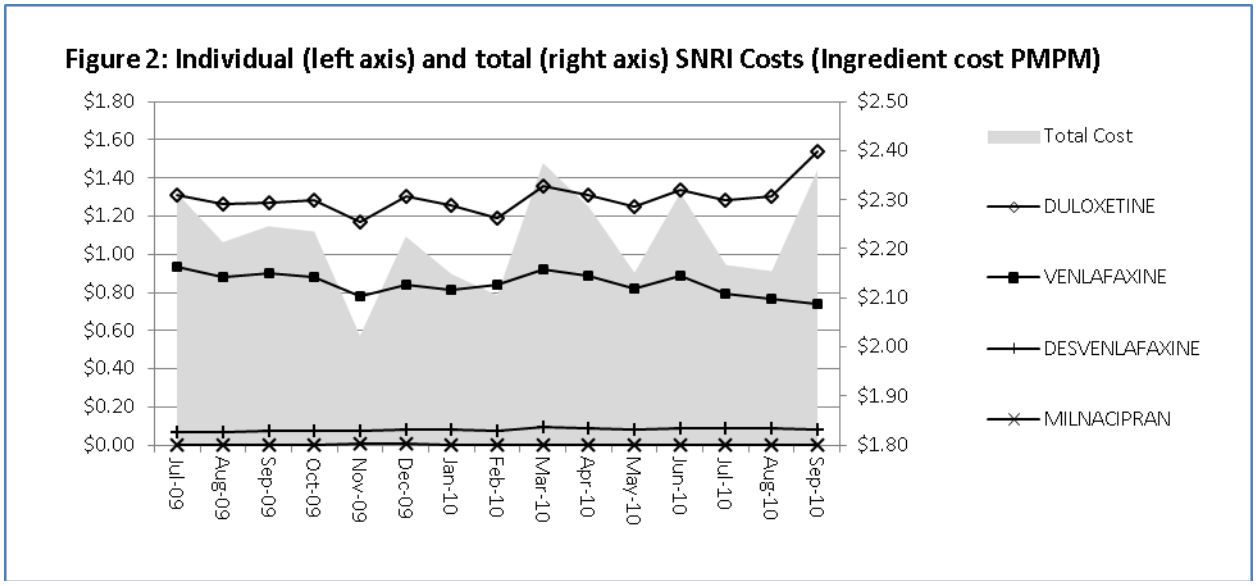


Table 4: SNRI 3rd Quarter 2010 Trend Summary

	% Change Q3 2009 to Q3 2010		Q3 2010 Costs		
	PMPM Utilization	**PMPM Cost**	**Total Cost**	**(%)**	**Avg Cost/ 30 Days**
DULOXETINE	2.8%	7.3%	$1,876,604	61.7%	$181
VENLAFAXINE	-7.6%	-15.6%	$1,044,118	34.3%	$148
DESVENLAFAXINE	22.3%	27.9%	$119,110	3.9%	$126
MILNACIPRAN	-40.9%	-46.7%	$1,411	0.0%	$101
Total:	**-0.8%**	**-1.3%**	**$3,041,243**	**100.0**	**$166**

SNRI User Analysis

A total of 11,208 unique patients had at least one fill for an SNRI from July 2009 – September 2010, of which 6,353 (~57%) were considered a chronic user of an SNRI. The demographics, shown in table 5, suggest that the two groups were similar in terms of measurable patient characteristics. The mean age was 41 years, however the range was from the very young (<1) to the very old (91). Racial and gender breakdown are consistent with overall population characteristics.

Table 5: Demographics of all SNRI users and chronic users

	All Users		Chronic Users	
Total	11,208	(%)	6,353	(%)
Age				
Mean	41		43	
Range	<1-91		9-83	
<6	2	0.0%	0	0.0%
6-12	18	0.2%	11	0.2%
13-18	312	2.8%	131	2.1%
19-65	10,855	96.9%	6,200	97.6%
>65	21	0.2%	11	0.2%
Female	8,983	80.1%	5,081	80.0%
Race				
White	9,545	85.2%	5,529	87.0%
Hispanic	1	0.0%	1	0.0%
American Indian	268	2.4%	153	2.4%
Black	297	2.6%	140	2.2%
Asian	86	0.8%	51	0.8%
Other	1,011	9.0%	479	7.5%

Most chronic SNRI users were taking duloxetine (58.3%), followed by venlafaxine (41.2%), and topiramate (25%). Table 6 summarizes the distribution of specific SNRO use as well as the prevalence of any SNRI duplication. Less than 0.5 % of all chronic users used two different SNRIs concurrently for at least 90 days.

Table 6: Distribution of SNRI users among chronic users (>=90 days continuous therapy)

	Chronic Users:	
Drug	**6,353**	**(%)**
DULOXETINE	3,703	58.3%
VENLAFAXINE	2,619	41.2%
DESVENLAFAXINE	414	6.5%
MILNACIPRAN	15	0.2%
Duplicate Therapy	34	0.5%

Table 7 summarizes dosing of SNRIs. The overall number of subjects exceeding maximum doses was small.

Table 7: Average Daily Dose and Percent of Patients Exceeding Max Dose

	Max Dose	Patients w/ > Max Dose	(%)	Average Daily Dose (mg)
DULOXETINE	120mg/day	61	0.9%	59
VENLAFAXINE	375mg/day	46	1.0%	132
DESVENLAFAXINE	100mg/day	16	2.1%	60
MILNACIPRAN	200mg/day	0	0.0%	96

Table 8 summarizes the prevalence of specific diagnoses which are commonly treated, both on and off-label, with SNRIs. In general, the prevalence of diagnoses among all users and chronic users were similar. About 77% of chronic SNRI users had at least one diagnosis for a disease of interest. Between 27-36% of subjects had a diagnosis indicating depression or anxiety. Ten percent of patients had a diagnosis of bipolar disorder and 5% had a diagnosis code indicating diabetic neuropathy and <0.5% had herpetic or other neuropathic pain. Fibromyalgia and migraine were associated with 17% and 14% of chronic users. When the cohort was restricted to only the 34 patients who received duplicate SNRIs, the prevalence of major depression nearly doubled to 47% while the others remained relatively unchanged or decreased. venlafaxine and 10 desvenlafaxine users are associated with a fibromyalgia diagnoses.

Table 8: Diagnostic information of all, chronic and concurrent SNRI users (patients may be in >1 diagnostic group)

	All Users		>=90 Day Therapy		Duplicate Therapy	
n	11,208	(%)	6,353	(%)	34	(%)
Anxiety Disorders	4,032	36.0%	2,251	35.4%	8	23.5%
Depressive disorder NOS	3,897	34.8%	2,286	36.0%	12	35.3%
Major Depressive Disorder	2,872	25.6%	1,754	27.6%	16	47.1%
Fibromyalgia	1,730	15.4%	1,073	16.9%	4	11.8%
Diabetes with Neurological Manifestations	492	4.4%	346	5.4%	3	8.8%
Neuropathic Pain	51	0.5%	34	0.5%		0.0%
Herpes Zoster with Nervous System Complications	21	0.2%	14	0.2%		0.0%
Any DX	7,912	70.6%	4,603	72.5%	26	76.5%

Table 9 summarizes the prevalence of specific diagnoses among chronic drug users by drug. These data indicate that >45% of desvenlafaxine users are associated with depression or anxiety; whereas <35% venlafaxine and duloxetine are associated with the same diagnoses. Nearly 87% of milnacipran users, 22% of duloxetine users , 11% of venlafaxine and 10% of desvenlafaxine are associated with fibromyalgia.

Table 9: Diagnostic information for chronic SNRI users by drug

	DULOXETINE		VENLAFAXINE		DESVENLAFAXINE		MILNACIPRAN	
n =	3,703		2,619		414		15	
Any Dx	2766	74.7%	1836	70.1%	326	78.7	13	86.7%
Anxiety Disorders	1,318	35.6%	921	35.2%	178	43.0%	3	20.0%
Depressive disorder NOS	1,276	34.5%	1,023	39.1%	187	45.2%	1	6.7%
Major Depressive Disorder	1,082	29.2%	692	26.4%	142	34.3%	4	26.7%
Fibromyalgia	811	21.9%	297	11.3%	41	9.9%	13	86.7%
Diabetes with Neurological Manifestations	260	7.0%	98	3.7%	11	2.7%		0.0%
Neuropathic Pain	21	0.6%	13	0.5%	2	0.5%	1	6.7%
Herpes Zoster with Nervous System Complications	8	0.2%	6	0.2%	1	0.2%		0.0%

Finally, table 10 shows the proportion of chronic users who were prescribed an SNRI by prescriber specialty.

Table 10: Chronic Patients by Prescriber Specialty

(patients may have >1 prescriber)

	Psychiatry Providers		Pain Providers		Primary Care		Total
DULOXETINE	497	13.4%	110	3.0%	1,952	52.7%	3,703
VENLAFAXINE	326	12.4%	59	2.3%	1,527	58.3%	2,619
DESVENLAFAXINE	80	19.3%	2	0.5%	167	40.3%	414
MILNACIPRAN	0	0.0%	1	6.7%	11	73.3%	15

Discussion:
While the class utilization and cost remain flat overall, duloxetine cost continues to rise a ~7% annually and is associated with 62% of the market share by cost. Venlafaxine, at 34% market share, declined 7% in utilization and >15% in cost. This is likely due to both generic completion on price and movement to the follow-on product, desvenlafaxine. Milnacipran, at <0.5% market share, is restricted to Oregon Health Plan (OHP) covered indications by prior authorization and its only FDA indication is fibromyalgia, which is not covered by OHP.

Over 2% of SNRIs were prescribed chronically for adolescents. Eleven children under 13 years were prescribed an SNRI. There is little data to support the use of these drugs in pediatrics and SSRI antidepressants are recommended first-line, if needed. Less than 2% of subjects were dosed above recommended doses. Less than 0.5% of chronic users were on dual SNRI therapy with 47% having Major Depressive Disorder.

Nearly 87% of milnacipran users, 22% of duloxetine users, 11% of venlafaxine and 10% of desvenlafaxine are associated with fibromyalgia. Both of the other FDA approved products for fibromyalgia, pregablin and milnacipran, are prior authorized and there may be some movement to the other SNRIs for this non-covered indication.

Primary care providers are the predominant prescribers of SNRIs. It is difficult to draw conclusions from the provider specialty data.

Recommendation:
- Prior authorize all SNRIs for covered OHP indication.
- Exempt from prior authorization requirement any patient with a depression or anxiety diagnosis on a claim within 1 year of the drug claim.

Diagnosis Group	ICD9
Depressive disorder NOS	311xx
Major Depressive Disorder	2962x. 2963x
Anxiety disorders	300xx

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Appendix A

GenName	Str	GSN
DESVENLAFAXINE SUCCINATE	50 mg	63736
DESVENLAFAXINE SUCCINATE	100 mg	63737
DULOXETINE HCL	20 mg	57891
DULOXETINE HCL	30 mg	57892
DULOXETINE HCL	60 mg	57893
MILNACIPRAN HCL	12.5 mg	65086
MILNACIPRAN HCL	25 mg	65088
MILNACIPRAN HCL	50 mg	65089
MILNACIPRAN HCL	100 mg	65090
MILNACIPRAN HCL	12.5 mg	65091
VENLAFAXINE HCL	25 mg	46398
VENLAFAXINE HCL	37.5 mg	46399
VENLAFAXINE HCL	50 mg	46400
VENLAFAXINE HCL	75 mg	46401
VENLAFAXINE HCL	100 mg	46402
VENLAFAXINE HCL	37.5 mg	46403
VENLAFAXINE HCL	75 mg	46404
VENLAFAXINE HCL	150 mg	46405
VENLAFAXINE HCL	37.5 mg	64444
VENLAFAXINE HCL	75 mg	64445
VENLAFAXINE HCL	150 mg	64446
VENLAFAXINE HCL	225 mg	64447