



Therapeutic Class ReviewSM

Mental Health – 2nd Generation Antidepressants Class

December 2008

New Product for Review:

fluvoxamine CR (Luvox CR[®]) [Jazz]
 venlafaxine SR tablets [Osmotica]
 bupropion HBr (Aplenzin) [Biovail]

Dossier Provided by Manufacturer: No

Dossier Evaluation: N/A

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

Second-generation antidepressants

- Agents included as second-generation antidepressants include the following

Bupropion	Fluoxetine	Sertraline
Citalopram	Fluvoxamine	Trazodone
Desvenlafaxine (Pristiq)	Mirtazapine	Venlafaxine (generic, Effexor XR)
Duloxetine (Cymbalta)	Nefazodone	
Escitalopram (Lexapro)	Paroxetine	

- The review incorporates a large, previously published systematic evidence review.
- This review concluded that there is no single agent with a clear clinical advantage in all situations, and medication selection is determined by the unique patient circumstances.

Venlafaxine extended-release tablets

- Newly available venlafaxine extended-release tablets are designated as a tier-1 generic medication on the Regence preferred medication list/formulary.
- Venlafaxine extended-release **tablets** are bioequivalent to Effexor XR **capsules** based on FDA analysis. However, venlafaxine extended-release tablets are not automatically substitutable by the dispensing pharmacist because of the change in dosage form.

Bupropion Hydrobromide (Aplenzin)

- Bupropion HBr (Aplenzin) extended-release tablets are a new salt form of bupropion that has FDA marketing approval for the management of major depressive disorder.

- Bupropion HBr (Aplenzin) was approved using bioequivalence data to bupropion HCl; there were no additional clinical trials.

Fluvoxamine controlled release capsules (Luvox CR)

- Fluvoxamine controlled release capsules (Luvox CR) are the extended-release form of fluvoxamine capsules (Luvox, generic).
- Fluvoxamine controlled release capsules (Luvox CR) have FDA marketing approval for the treatment of obsessive-compulsive disorder and seasonal affective disorder.
 - Approval was primarily based on the clinical experience of fluvoxamine immediate release (Luvox) and three short-term trials using fluvoxamine controlled release capsules (Luvox CR).
 - There is no reliable comparative data.
- There are numerous generic alternatives for the management of both obsessive-compulsive disorder and seasonal affective disorder (see table on page 7).
- There are no head-to-head trials evaluating the effectiveness of fluvoxamine controlled release capsules (Luvox CR) against any other antidepressant for any other indication.

Evidence

- There is uncertain evidence from systematic reviews and randomized, controlled trials regarding the comparative efficacy of the second-generation antidepressants in the management of major depressive disorder and other affective psychiatric indications.
 - The selective serotonin reuptake inhibitors (SSRIs) appear to exhibit similar efficacy in the management of major depressive disorder.
 - Efficacy in other indications varies between agents and disorders, but there is no agent with a clear clinical advantage in all clinical situations.
 - There is uncertain evidence that serotonin-norepinephrine reuptake inhibitors (SNRIs) may result in a modest improvement in clinical response in the management of major depressive disorder, but this advantage appears to be accompanied by an increase in adverse events.
 - There have been no new comparative clinical studies evaluating desvenlafaxine (Pristiq) versus other antidepressants since the original review.
- Based on an analysis by the FDA, venlafaxine extended-release tablets appear to be bioequivalent to venlafaxine extended-release capsules (Effexor XR).
- There is no useful evidence that fluvoxamine controlled release capsules (Luvox CR) provides clinical advantage to any other formulary alternative in the management of obsessive-compulsive disorder, seasonal affective disorder, or any other indication.
- There is no useful evidence that bupropion HBr (Aplenzin) provides clinical advantage to any other formulary alternative in the management of major depressive disorder, or any other indication.

Decision

- Venlafaxine XR capsules (Effexor XR) are non-preferred/non-formulary because venlafaxine XR tablets can provide equal effectiveness at a lower cost to members.
- Fluvoxamine CR (Luvox CR) is non-preferred/non-formulary because there is no useful evidence that it provides clinical advantages over available generic and preferred/formulary alternatives.
- Bupropion HBr (Aplenzin) is non-preferred/non-formulary because there is no evidence of a clinical advantage over generic and preferred/formulary alternatives.

Products ^[1,2]

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)					
duloxetine (Cymbalta [®])	8/2004	6/2013	Major depressive disorder, Pain associated with diabetic peripheral neuropathy	60mg PO QD 60mg PO QD/BID	Pain management Stress urinary incontinence Fibromyalgia
venlafaxine immediate release (Effexor XR [®])	12/2003 10/1997	N/A 2010-2013	Major depressive disorder, Generalized Anxiety disorder, Social Anxiety disorder	75 mg PO twice daily 150mg PO daily	Atypical facial pain, Post-mastectomy pain syndrome, Colonic sensorimotor functions, Obsessive-compulsive disorder, Diabetic peripheral neuropathy Painful polyneuropathy ¹ , Bipolar depression, Premenstrual dysphoric disorder, Management of hot flushes, diabetic neuropathic pain, ⁴¹ Fibromyalgia ⁴⁹
desvenlafaxine (Pristiq [™])	02/2008	02/2022	Major depressive disorder,	50 mg PO daily	
Selective Serotonin Reuptake Inhibitors (SSRIs)					
citalopram	7/1998	N/A	Depression	40 mg PO daily	Headache Panic disorder
escitalopram (Lexapro [®])	8/2002	03/2012	Depression, Generalized anxiety disorders	20 mg PO daily	Anxiety with depression
fluoxetine Prozac Weekly [®]	12/1987 02/2001	N/A 05/2017	Depression, Bulimia nervosa, Obsessive-compulsive disorder, Panic disorder, Premenstrual dysphoric disorder	20mg PO daily 90mg PO QWk	Body dysphoric disorder, fibromyalgia, post-traumatic stress disorder, Raynaud's phenomenon
fluvoxamine fluvoxamine XR (Luvox CR [®])	12/1994 02/2008	N/A 02/2011	Obsessive-compulsive disorder	100 mg PO twice daily 150 mg PO daily	Depression, Autism, Panic disorder, Social anxiety disorder
paroxetine	12/1992	N/A	Same as sertraline (Zoloft) and generalized anxiety disorder	20 mg PO daily	Pathological gambling
sertraline	12/1991	N/A	Depression, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social anxiety disorder	100 mg PO daily	dysthymia
Tricyclic Antidepressants (TCAs)					
amitriptyline	4/1961	N/A	Depression w/ anxiety	150 mg PO daily	polyneuropathy, diabetic neuropathic pain, fibromyalgia
desipramine	10/1964	N/A	Depression	150mg PO daily	Attention deficit disorder, Diabetic neuropathic pain
imipramine	5/1984	N/A	Depression Enuresis (children)	100mg PO daily	Panic disorder, diabetic neuropathic pain, urinary incontinence
Dopamine reuptake inhibitors					
bupropion bupropion SR bupropion XL	12/1985 10/1996 8/2003	N/A N/A N/A	Depression, smoking cessation	100mg PO TID 150mg PO BID 300mg PO QD	

Products (Continued) ^[1,2]

Drug Products	FDA approval^a	Patent Expiration(s)^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses^c
Monoamine Oxidase Inhibitors (MAOI's)					
isocarboxazid (Marplan)	7/1959	N/A	Depression	20mg PO BID	Dyskinesia, eating disorder, exogenous obesity, orthostatic hypotension, trichotillomania
phenelzine sulfate (Nardil)	6/1961	N/A	Depression	15mg PO TID	Agoraphobia, Bulimia nervosa, Crohn's disease, Globus hystericus, Headache, Narcolepsy, Obsessive-compulsive disorder, Orthostatic hypotension, Panic disorder, Posttraumatic stress disorder, Social phobia
tranylcypromine sulfate	2/1961	N/A	Depression	10mg PO TID	Panic disorder, Dismorphophobia, Obsessive-compulsive disorder, Seasonal affective disorder, Social phobia, Subcortical leukoencephalopathy
Selegiline transdermal system (Emsam)	02/2006	06/2018	Depression	6mg to 12mg applied topically each day.	Smoking cessation, HIV-associated cognitive impairment, cocaine addiction, ADHD

^a Date applies to approval date for the original brand name medication where there are now generics available.

^c Based on patents listed in Orange Book as of 09/2008.

^d As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

FDA-approved indications for selected antidepressants.^[1-15]

Indication	Selective Serotonin Reuptake Inhibitors (SSRIs)						Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)			Miscellaneous		
	citalopram	fluoxetine	fluvoxamine	paroxetine	sertraline	Lexapro	Effexor XR	Pristiq	Cymbalta	Bupropion SR	Wellbutrin XL	mirtazapine
Depression	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Generalized anxiety disorder				✓		✓	✓		✓			
Obsessive-compulsive disorder		✓	✓	✓	✓							
Panic disorder		✓		✓	✓		✓					
Premenstrual dysphoric disorder		✓		✓	✓							
Posttraumatic stress disorder				✓	✓							
Social anxiety disorder				✓	✓		✓					
Bulimia Nervosa		✓										
Seasonal Affective Disorder											✓	

✓ = FDA approved indication Medications in **BOLD** are generically available.

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