



Therapeutic Class ReviewSM

Mental Health – Paliperidone (InvegaTM Extended-Release Tablets)

April 2007

New Product for Review:

Paliperidone (InvegaTM) [Ortho-McNeil Janssen]

Dossier Provided by Manufacturer:

Dossier Evaluation: 3

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Executive Summary

- Schizophrenia is a debilitating mental illness that affects about one percent of the population.
 - Antipsychotic medication is the mainstay of treatment for this condition.
 - Adverse events and/or loss of efficacy related to individual agents often results in frequent therapy changes.
 - There is an unmet need for reliably effective antipsychotic medications with low incidence of troublesome side effects.
- Paliperidone (Invega) is a psychotropic agent classified as an atypical antipsychotic.
 - Paliperidone (Invega) is indicated for the treatment of schizophrenia based on trials of up to 6 weeks in duration.
 - Paliperidone is the major active metabolite of risperidone (Risperdal).
- Paliperidone (Invega) is dosed as 6 mg each morning without the need for dose titration.
 - The dose must be individualized for renal impairment.
 - No dose adjustment is needed for liver impairment.

Evidence

- None of the trials evaluating the efficacy of paliperidone (Invega) in the management of patients with schizophrenia were useful or possibly useful.
- There are no head-to-head trials comparing either the safety or efficacy of paliperidone (Invega) to other typical or atypical antipsychotics for the management of patients with schizophrenia.
- Considerations in Subpopulations:
 - **Pediatrics** - The safety and effectiveness of paliperidone (Invega) in pediatric patients has not been established.
 - **Geriatrics**: No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. Dosage must be adjusted for decreased renal function.

- **Gender:** No dosage adjustment is necessary based on gender.
- **Race, ethnicity:** No dosage adjustment is necessary based on race or ethnicity.

Decision

Paliperidone (Invega) is non-preferred/non-formulary because:

- It has unproven advantages compared to current formulary alternatives; and
- There is a lack of long-term safety data with this product.

Products^[1-3]

Drug Products	FDA approval ^a	Patent Expiration(s) ^d	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
clozapine (Clozaril [®] , generic)	09/1989	N/A	- Tx resistant schizophrenia - Suicidal behavior, recurrent	400 mg daily PO	- Aggressive behavior - Bipolar disorder - Borderline personality disorder - Dementia - Excessive thirst - HIV psychosis disorder - Involuntary movement disorder - Parkinson's disease – psychotic disorder - Schizoaffective disorder, Refractory
risperidone (Risperdal [®])	12/1993	12/2007	- Schizophrenia - Bi-polar mania - Irritability in autism	4 - 8 mg daily PO 25 mg/q 2wk IM	- Behavioral syndrome – Dementia - Behavioral syndrome - Mental retardation - Bipolar disorder - Borderline personality disorder - Cocaine dependence - Cognitive function finding - Delusional disorder - Dementia - Psychotic disorder - Depression, Refractory - Drug-induced psychosis - Levodopa adverse reaction - Gilles de la Tourette's syndrome - Huntington's disease - Obsessive-compulsive disorder, Refractory - Organic psychotic condition - Parkinson's disease - Psychotic disorder - Pervasive developmental disorder - Posttraumatic stress disorder - Schizotypal personality disorder - Stuttering - Trichotillomania
olanzapine (Zyprexa [®])	09/1996	04/2011	- Schizophrenia - Bi-polar mania	5 mg – 20 mg daily PO 2.5-10 mg IM	- Cannabis induced psychotic disorder - Alzheimer's disease - Psychotic disorder - Anorexia nervosa - Anxiety – Dementia - Borderline personality disorder - Cancer – Nausea - Cocaine dependence - Delirium - Depressed bipolar I disorder - Drug-induced psychosis - Methamphetamine adverse reaction - Essential tremor - Gilles de la Tourette's syndrome - Headache

Drug Products	FDA approval ^a	Patent Expiration(s) ^d	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
					- Huntington's disease - Neuroleptic adverse reaction – Tremor - Obsessive-compulsive disorder, Refractory - Parkinson's disease - Psychotic disorder - Pervasive developmental disorder - Posttraumatic stress disorder - Repetitive self-excoriation - Schizophrenic prodrome
olanzapine (Zyprexa [®]) - continued					- Senile dementia of the Lewy body type - Severe major depression with psychotic features - Trichotillomania
quetiapine (Seroquel [®])	09/1997	09/2011	- Schizophrenia - Bi-polar mania	400 mg – 800 mg daily PO	- Bipolar disorder - Delirium - Diffuse Lewy body disease - Psychotic disorder - Gilles de la Tourette's syndrome - Obsessive-compulsive disorder - Parkinson's disease - Psychotic disorder - Tardive dyskinesia
ziprasidone (Geodon [®])	02/2001	03/2012	- Schizophrenia - Bi-polar mania	20 mg – 80 mg BID PO 10-20 mg/day IM	- Major depressive disorder, Treatment-resistant; Adjunct - Schizoaffective disorder
aripiprazole (Abilify [®])	11/2002	10/2014	- Schizophrenia - Bi-polar mania	10 mg – 30 mg daily PO	- Asperger's disorder
paliperidone (Invega [™])	12/2006	10/2009	- Schizophrenia	3 mg to 12 mg daily PO	- None identified
For Comparison					
haloperidol (Haldol, generic)	04/1967	N/A	- Schizophrenia	0.5 mg to 10 mg BID to TID	- Numerous
perphenazine (Trilafon, generic)	02/1957	N/A	- Schizophrenia - Nausea/vomiting	4 mg to 16 mg TID	- Numerous

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

^c As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

^d Based on patents listed in Orange Book as of January 2007

References

1. Klasco RK (Ed): DRUGDEX[®] System (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: <http://www.thomsonhc.com> (cited: 3/5/07).
2. Invega[™] [package insert]. Titusville, NJ: Janssen, L.P. December 2006.
3. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2006. Available from Wolters Kluwer Health, Inc. Accessed March 5, 2007.
4. Kane J, Canas F, Kramer M, Ford L, Gassmann-Mayer C, et al. Treatment of schizophrenia with paliperidone extended-release tablets: A 6-week placebo-controlled trial. *Schizophr Res*. 2007 Feb;90(1-3):147-61.

5. Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and effect on functioning of paliperidone extended-release tablets in schizophrenia: an international 6-week placebo-controlled study [poster]. Ortho-McNeil Janssen Product Dossier: Invega™ (Paliperidone), Ortho-McNeil Janssen, LLC., Titusville, NJ. Data reviewed March 5, 2007.
6. Marder S, Kramer M, Ford L, Eerdekens E, Lim P, Eerdekens M. A 6-week, US-based placebo-controlled study on the efficacy and tolerability of two fixed dosages of oral paliperidone extended-release tablets in the treatment of acute schizophrenia [poster]. Ortho-McNeil Janssen Product Dossier: Invega™ (Paliperidone), Ortho-McNeil Janssen, LLC., Titusville, NJ. Data reviewed March 5, 2007.
7. Kramer M, Simpson G, Maciulis V, Kushner S, Vijapurkar U, Lim P, et al. Paliperidone Extended-Release Tablets for Prevention of Symptom Recurrence in Patients With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study. *J Clin Psychopharmacol*. 2007 Feb;27(1):6-14.
8. Kramer M, Ford L, Gassmann-Mayer C, Lim P, Eerdekens M. A 6-week placebo-controlled study on the safety and tolerability of flexible doses of oral paliperidone extended-release tablets in the treatment of schizophrenia in elderly patients. [poster] Ortho-McNeil Janssen Product Dossier: Invega™ (Paliperidone), Ortho-McNeil Janssen, LLC., Titusville, NJ. Data reviewed March 5, 2007.
9. Economic Modeling Report. Ortho-McNeil Janssen Product Dossier: Invega™ (Paliperidone), Ortho-McNeil Janssen, LLC., Titusville, NJ. Data reviewed March 5, 2007.
10. Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. The Cochrane Database of Systematic Reviews: Reviews 2005 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003729.pub2 YR: 2005. NO: 2.
11. Duggan L, Fenton M, Rathbone J, Dardennes R, El-Dosoky A, Indran S. Olanzapine for schizophrenia. *Cochrane Database Syst Rev*. 2005 Apr 18;(2):CD001359. Review. PMID: 15846619.
12. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. The Cochrane Database of Systematic Reviews: Reviews 2004 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004578.pub2 YR: 2004. NO: 2.
13. Jayaram MB, Hosalli P. Risperidone versus olanzapine for schizophrenia. The Cochrane Database of Systematic Reviews: Reviews 2005 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD005237 YR: 2005. NO: 2.
14. Marriott RG, Neil W, Waddingham S. Antipsychotic medication for elderly people with schizophrenia. The Cochrane Database of Systematic Reviews: Reviews 2006 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD005580 YR: 2006. NO: 1.
15. Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. The Cochrane Database of Systematic Reviews: Reviews 2006 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000459.pub2 YR: 2006. NO: 1.
16. Srisurapanont M, Maneeton B, Maneeton N. Quetiapine for schizophrenia. The Cochrane Database of Systematic Reviews: Reviews 2004 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000967.pub2 YR: 2004. NO: 2.
17. Lawrie S, McIntosh A, Nadeem Z. Schizophrenia. *Clin Evid*. 2005 Dec;(14):1306-30.
18. Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association (APA). *Am J Psychiatry* 1997 Apr;154(4 Suppl):1-63.
19. Veterans Administration, Department of Defense. Management of persons with psychoses. Washington (DC): Department of Veteran Affairs; 2004 May. Various p. Available at: http://www.ngc.gov/summary/summary.aspx?doc_id=5632&nbr=003794&string=schizophrenia. Accessed: March 5, 2007.
20. Risperdal® [package insert]. Titusville, NJ: Janssen, L.P. December 2006.
21. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al.; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005 Sep 2;353(12):1209-23.