Preferred Drug List

NEW DRUG REVIEW

Proprietary Name: Fanapt™

Common Name: Iloperidone

PDL Category: Antipsychotics-Atypicals

Comparable Products	Preferred Drug List Status
Abilify®	**Preferred**
Risperidone	**Preferred**
Zyprexa®	**Preferred**

Indications and Usage: Acute treatment of schizophrenia in adults. [1]

Mechanism of Action: Exact mechanism of action is unknown. It has been suggested that the efficacy of Fanapt™ in schizophrenia is mediated through a combination of antagonist activity at D2 and 5-HT_2A receptors.[1]

Metabolism: Iloperidone is metabolized by both CYP3A4 and CYP2D6. Drugs that inhibit either of these enzymes when taken concomitantly with iloperidone may inhibit metabolism and increase blood levels of iloperidone. Specifically, ketoconazole and itraconazole are potent CYP3A4 inhibitors. When used concomitantly with iloperidone, doses of iloperidone should be reduced by one-half. Paroxetine and fluoxetine are potent CYP2D6 inhibitors and dose of iloperidone should be reduced by one-half when used in combination with either of these agents. Lastly, there have been reports of QTc prolongation of 9msec at a 12mg BID dose. Therefore, it is recommended that the combination of iloperidone with other drugs known that prolong the QTc interval be avoided.[1]

Dosage Forms: Tablets: 1mg, 2mg, 4mg, 6mg, 8mg, 10mg and 12mg[1]

Recommended Dosage: The recommended target dose is 12 to 24mg/day administered twice daily. Target dose is achieved by daily dose adjustments, starting at a dose of 1mg twice daily, to reach the 12mg/day to 24mg/day dose range.[1]

Common Adverse Drug Reactions: *All % for listed adverse events are given as the extent that they exceed placebo in clinical trials using 10-16mg/day*. Fatigue (1%), Dizziness (3%), Somnolence (4%), Tremor (1%), Extrapyramidal Disorder (1%), Lethargy (2%), Orthostatic Hypotension (2%), Tachycardia (2%), Blurred vision (1%), Nausea (0%), Dry mouth (7%), Diarrhea (1%), Nasopharyngitis (1%), Upper Respiratory Tract Infection (1%), Nasal Congestion (3%), Dyspnea (>1%), Ejaculation Failure (>1%), Increased weight (0%), Rash (1%). Mean changes in baseline for total cholesterol is-3.9 for Fanapt™ vs -7.7 for placebo. Specific EPS events include: Akathisia (0%), Bradykinesia (0.6%), Dyskinesia (0.2%), Dystonia (0.3%), Parkinsonism (0.2%), Tremor (0.6%). Orthostatic hypotension, mediated by blockade of alpha 1 receptors, may be decreased by slow upwards dosage titration. In clinical trials with adults with schizophrenia, EPS-related events excluding akathisia was 1%; akathisia-related events was 4%. Tardive dyskinesia, a potentially irreversible movement disorder as well as NMS (neuroleptic malignant syndrome), have been reported with medications within this class of agents. With regard to weight gain, dose dependent increases in weight, defined as ≥ 7 %, was noted. Pooling data from four placebo controlled trials of 4 to 6 weeks duration, weight gain occurred in 12 % of subjects treated with Fanapt™ 10-16 mg/day and 18 % for subjects receiving 20 to 24 mg/day. Across all short and long term studies, the overall mean change from baseline at endpoint was 2.1 kg. Hyperglycemia, diabetes, and metabolic syndrome have been associated with other second generation antipsychotics. Patients with risk factors for diabetes (eg obesity, family history of diabetes) should undergo blood glucose testing at the initiation of treatment and periodically during treatment.

Fanapt™, in a pooled analysis of three trials, demonstrated a statistically significant dose-dependent increase in the QT interval at all doses studied (up to 9 msec at 20-24 mg/day). Avoid use of Fanapt™ in combination with other drugs that are

known to prolong QTc; use caution and consider dose modification when prescribing Fanapt™ with other drugs which inhibit Fanapt™ metabolism. [1]

Contraindications: None[1]

Manufacturer: Vanda Pharmaceuticals, Inc.

Summary

Analysis: Fanapt™ is only one of two new second-generation antipsychotics approved by the FDA since 2006. Iloperidone belongs to the chemical class of piperidinyl-benzisoxazole derivatives, and is a psychotropic agent that is postulated to work through blockade at dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) receptors. As with all antipsychotics, Fanapt™ has a black box warning alerting the potential for increased mortality in elderly patients with dementia-related psychosis. Most of the reported deaths were cardiovascular or infectious in nature.

Iloperidone was originally developed in 1990 by Hoechst-Roussel Pharmaceuticals. In 1997, Titan Pharmaceuticals purchased rights to this drug and sublicensed it in 1998 to Novartis. Novartis performed three clinical trials that suggested iloperidone may be less efficacious than haloperidol and risperidone and sold it to Vanda Pharmaceuticals in 2004. In study one, patients were assigned to one of five groups including placebo, Fanapt™ 8 mg/day, Fanapt™ 10 mg/day, Fanapt™ 12 mg/ day, or Haldol 15 mg/day. Only the high dose Fanapt™ arm (12 mg/day) and the active comparator, Haldol ®15 mg/day, separated from placebo on the primary outcome, change in total PANSS score from baseline (Positive and Negative Symptom Scale). In study 2 and 3, higher doses of Fanapt™ (up to 20 mg/day) were compared to risperidone (up to 8 mg/day) or placebo. In these studies, Fanapt™ outperformed placebo in three of four doses tested whereas risperidone separated from placebo at both study doses. These studies were performed to determine safety and efficacy. One 6 week placebo- and active-comparator controlled randomized clinical trial to obtain FDA approval demonstrated that iloperidone was superior to placebo in regards to the Brief Psychiatric Rating Scale (BPRS) total score for both dosage ranges (12-16mg/day and 20-24mg/day); however, during the first two weeks of the trial the active-control was superior to iloperidone. A possible explanation may be due to the more rapid titration that is allowed with the active comparator, since recommendations for iloperidone suggest a slower dose titration. A second 4 week trial also included a placebo- and active-comparator control, but the primary endpoint was the change from baseline on the Positive and Negative Syndrome Scale (PANSS). Results of this study showed that iloperidone 24mg/day was superior to placebo in the PANSS total score. Compared to the active control, iloperidone had similar efficacy. Both of these short term studies (6 and 4 weeks) led to FDA approval; however, use beyond 6 weeks has not been systematically studied. Overall, it appears that higher doses of Fanapt™ are required for efficacy in schizophrenia. Careful dose titration is required to achieve therapeutic dosages and avoid potentially problematic orthostatic hypotension.

Fanapt™ is chemically related to risperidone and its' efficacy appears to be similar to the other second generation antipsychotics. In comparing its side effect profile to the other atypical agents, the diabetes risk appears comparable to risperidone and Seroquel® ("average"), EPS comparable to Abilify® and Zyprexa® (less than "average'), hyperprolactinemia less than risperidone and comparable to Abilify®, Zyprexa®, and Seroquel® (less than "average"), QTc prolongation comparable to Geodon™ (high) and weight gain less than Zyprexa®, Seroquel® and risperidone and comparable to Invega® but greater than Abilify®. On balance it is no more effective than the other atypical choices but it may provide another less metabolically damaging and cost-effective management choice for physicians. Its BID schedule and titration schedule will be significant self-limiting characteristics. Its mix of side effect profile differences would appear to warrant preferential treatment.

Therefore, it is recommended that Fanapt™ be preferred.

IME Recommendation:

☒ Preferred Drug ☐ Recommended Drug

☐ Non-Preferred Drug ☐ Non-Recommended Drug

☐ Preferred Drug with Conditions

1. Fanapt™ [package insert]. Rockville, MD: Vanda Pharmaceuticals, Inc.; 2010.
2. Citrome L. Iloperidone for schizophrenia: a review of the efficacy and safety profile for this newly commercialized second-generation antipsychotic. *Int J Clin Pract*. 2009; 63(8): 1237-48.