

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

LABELING

FANAPT™

(iloperidone) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FANAPT safely and effectively. See full prescribing information for FANAPT.

FANAPT™ (iloperidone) tablets

Initial U.S. Approval: 2009

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. FANAPT is not approved for use in patients with dementia-related psychosis. (5.1)

INDICATIONS AND USAGE

FANAPT is an atypical antipsychotic agent indicated for the acute treatment of schizophrenia in adults (1). In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

DOSEAGE AND ADMINISTRATION

The recommended target dosage of FANAPT tablets is 12 to 24 mg/day administered twice daily. This target dosage range is achieved by daily dosage adjustments, alerting patients to symptoms of orthostatic hypotension, starting at a dose of 1 mg twice daily, then moving to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7 respectively, to reach the 12 mg/day to 24 mg/day dose range. FANAPT can be administered without regard to meals. (2.1)

DOSEAGE FORMS AND STRENGTHS

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets. (3)

CONTRAINDICATIONS

Known hypersensitivity to FANAPT or to any components in the formulation. (4)

WARNINGS AND PRECAUTIONS

- **Elderly patients with dementia-related psychosis who are treated with atypical antipsychotic drugs are at an increased risk of death and cerebrovascular-related adverse events, including stroke.** (5.1)
- **QT prolongation:** Prolongs QT interval and may be associated with arrhythmia and sudden death—consider using other antipsychotics first. 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 that inhibit FANAPT metabolism. Monitor serum potassium and magnesium in patients at risk for electrolyte disturbances (1, 5.2, 7.1, 7.3, 12.3)

- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation of drug and close monitoring. (5.3)
- **Tardive dyskinesia:** Discontinue if clinically appropriate. (5.4)
- **Hyperglycemia and diabetes mellitus:** Monitor glucose regularly in patients at risk for diabetes. (5.5)
- **Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.7)
- **Orthostatic hypotension:** Dizziness, tachycardia, and syncope can occur with standing. (5.8)
- **Leukopenia, Neutropenia, and Agranulocytosis** have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors. (5.9)
- **Suicide:** Close supervision of high risk patients. (5.13)
- **Priapism:** Cases have been reported in association with FANAPT treatment. (5.14)
- **Potential for cognitive and motor impairment.** Use caution when operating machinery. (5.15)
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS.**

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence $\geq 5\%$ and two-fold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vanda Pharmaceuticals at 1-888-46VANDA (1-888-466-2632) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- The dose of FANAPT should be reduced in patients co-administered a strong CYP2D6 or CYP3A4 inhibitor. (2.2, 7.1)
- **Pregnancy:** No human or animal data. Use only if clearly needed. (8.1)
- **Nursing Mothers:** Should not breast feed. (8.3)
- **Pediatric Use:** Safety and effectiveness not established in children and adolescents. (8.4)
- **Hepatic Impairment:** Not recommended for patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

1 INDICATIONS AND USAGE

2 DOSEAGE AND ADMINISTRATION

- 2.1 Usual Dose
- 2.2 Dosage in Special Populations
- 2.3 Maintenance Treatment
- 2.4 Reinitiation of Treatment in Patients Previously Discontinued
- 2.5 Switching From Other Antipsychotics

3 DOSEAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis
- 5.2 QT Prolongation
- 5.3 Neuroleptic Malignant Syndrome (NMS)
- 5.4 Tardive Dyskinesia
- 5.5 Hyperglycemia and Diabetes Mellitus
- 5.6 Weight Gain
- 5.7 Seizures
- 5.8 Orthostatic Hypotension and Syncope
- 5.9 Leukopenia, Neutropenia and Agranulocytosis
- 5.10 Hyperprolactinemia
- 5.11 Body Temperature Regulation
- 5.12 Dysphagia
- 5.13 Suicide
- 5.14 Priapism
- 5.15 Potential for Cognitive and Motor Impairment

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience

7 DRUG INTERACTIONS

- 7.1 Potential for Other Drugs to Affect FANAPT
- 7.2 Potential for FANAPT to Affect Other Drugs
- 7.3 Drugs that Prolong the QT Interval

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and delivery
- 8.3 Nursing mothers
- 8.4 Pediatric use
- 8.5 Geriatric use
- 8.6 Renal impairment
- 8.7 Hepatic impairment
- 8.8 Smoking Status

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled substance
- 9.2 Abuse

10 OVERDOSAGE

- 10.1 Human experience
- 10.2 Management of overdose

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, mutagenesis, impairment of fertility

14 CLINICAL STUDIES

15 HOW SUPPLIED/STORAGE AND HANDLING

16 PATIENT COUNSELING INFORMATION

- 17.1 QT Interval Prolongation
- 17.2 Neuroleptic Malignant Syndrome
- 17.3 Orthostatic Hypotension

17.4 Interference with Cognitive and Motor Performance
17.5 Pregnancy
17.6 Nursing
17.7 Concomitant Medication

17.8 Alcohol
17.9 Heat Exposure and Dehydration
***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristics(s) of the patients is not clear. FANAPT is not approved for the treatment of patients with Dementia-Related Psychosis. *[see Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

FANAPT™ tablets are indicated for the acute treatment of adults with schizophrenia *[see Clinical Studies (14)]*.

When deciding among the alternative treatments available for this condition, the prescriber should consider the finding that FANAPT is associated with prolongation of the QTc interval *[see Warnings and Precaution (5.2)]*. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether FANAPT will cause torsade de pointes or increase the rate of sudden death is not yet known.

Patients must be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the acute treatment of schizophrenia *[See Dosage and Administration (2.1) and Clinical Studies (14)]*.

The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[See Dosage and Administration (2.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dose

FANAPT must be titrated slowly from a low starting dose to avoid orthostatic hypotension due to its alpha-adrenergic blocking properties. The recommended starting dose for FANAPT tablets is 1 mg twice daily. Increases to reach the target dose range of 6-12 mg twice daily may be made with daily dosage adjustments to 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. Efficacy was demonstrated with FANAPT in a dose range of 6 to 12 mg twice daily. Prescribers should be mindful of the fact that patients need to be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require similar titration. Prescribers should also be aware that some adverse effects associated with FANAPT use are dose related.

The maximum recommended dose is 12 mg twice daily (24 mg/day); FANAPT doses above 24 mg/day have not been systematically evaluated in the clinical trials.

FANAPT can be administered without regard to meals.

2.2 Dosage in Special Populations

Dosage adjustments are not routinely indicated on the bases of age, gender, race, or renal impairment status [see *Use in Specific Populations* (8.6, 8.7)].

Dosage adjustment for patients taking FANAPT concomitantly with potential CYP2D6 inhibitors: FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors such as fluoxetine or paroxetine. When the CYP2D6 inhibitor is withdrawn from the combination therapy, FANAPT dose should then be increased to where it was before [See *Drug Interactions* (7.1)].

Dosage adjustment for patients taking FANAPT concomitantly with potential CYP3A4 inhibitors: FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is withdrawn from the combination therapy, FANAPT dose should be increased to where it was before [See *Drug Interactions* (7.1)].

Hepatic Impairment: FANAPT is not recommended for patients with hepatic impairment.

2.3 Maintenance Treatment

Although there is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained, it is generally recommended that responding patients be continued beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.4 Reinitiation of Treatment in Patients Previously Discontinued


Although there are no data to specifically address re-initiation of treatment, it is recommended that the initiation titration schedule be followed whenever patients have had an interval off FANAPT of more than 3 days.

2.5 Switching From Other Antipsychotics

There are no specific data to address how patients with schizophrenia can be switched from other antipsychotics to FANAPT or how FANAPT can be used concomitantly with other antipsychotics. Although immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

3 DOSAGE FORMS AND STRENGTHS

FANAPT tablets are available in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg.

The tablets are white, round, flat, beveled-edge and identified with a logo  debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side.

4 CONTRAINDICATIONS

FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. FANAPT is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 QT Prolongation

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.