

Serotonin Flags Progression of Heart Failure

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FROM THE ANNUAL MEETING
OF THE HEART FAILURE
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SAN DIEGO – Plasma levels of serotonin were significantly elevated in patients with decompensated systolic heart failure, compared with patients in the compensated state and with normal controls, according to a single-center study.

The finding suggests that serotonin has an active role in the progression of heart failure, researchers led by Dr. Ahmed M. Selim wrote in a poster at the meeting.

“More studies should be done to test the sensitivity, specificity, and prognostic value of serotonin as a marker for congestive heart failure and also to investigate the therapeutic benefits of the medications affecting this pathway,” noted the researchers of the cardiology de-

partment at Albert Einstein College of Medicine, New York.

Dr. Selim and his associates collected plasma serotonin levels from 29 patients who were admitted with decompensated heart failure, 61 patients with stable heart failure, and 22 normal controls. They excluded patients on medications affecting serotonin receptors and those with pulmonary hypertension. All heart failure patients were on stable doses of medica-

tions and had left-ventricular ejection fractions of 40% or less; controls had a mean ejection fraction of 59%. Patients' mean age was 55 years; 62% were male.

The mean serotonin level in controls was 2.4 ng/mL, vs. 4.1 ng/mL in the compensated group and 11.8 ng/mL in the decompensated group, independent of age, race, renal function, diabetes, and hypertension. “All results were highly significant,” the researchers wrote. ■

FANAPT™ (*iloperidone*) tablets

Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for 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 characteristic(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)* in the full prescribing information].

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 Precautions (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)* in the full prescribing information].

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)* in the full prescribing information].

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.

The use of FANAPT should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalolol) antiarrhythmic medications, anti-psychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism [see *Drug Interactions (7.1)*], and in patients with reduced activity of CYP2D6 [see *Clinical Pharmacology (12.3)* in the full prescribing information].

It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. FANAPT should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 ms.

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysarrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of this syndrome should include: (1) immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, which may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely on prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.