

# Glatiramer Acetate May Delay Progress to MS

BY ROBERT FINN

**G**latiramer acetate significantly delayed the conversion of clinically isolated syndrome to clinically definite multiple sclerosis, according to a randomized, double-blind, placebo-controlled trial published in the *Lancet*.

The drug reduced the risk of developing clinically definite multiple sclerosis (MS) by 45% compared with placebo,

wrote Dr. Giancarlo Comi of the University Vita-Salute, Milan, and his coinvestigators from the PreCISE study (*Lancet* 2009[doi:10.1016/S0140-6736(09)61259-9]). In addition, the time it took for 25% of patients to convert to clinically definite disease more than doubled, from 336 days for placebo to 722 days for glatiramer acetate.

Glatiramer acetate previously has been shown to reduce relapses in patients

with the relapsing-remitting form of MS.

In 85% of patients who are eventually diagnosed with MS, the first clinical event is an acute episode that goes away on its own. This is known as a clinically isolated syndrome. Not everyone who experiences a clinically isolated syndrome goes on to develop MS. After 15-20 years, about half of these patients will have major locomotor disabilities, but about a third will have little or no dis-

ability, Dr. David H. Miller of University College London, and Dr. Siobhan M. Leary of the National Hospital for Neurology and Neurosurgery, London, noted in a commentary (*Lancet* 2009 [doi:10.1016/S0140-6736(09)61453-7]).

Beta interferon also has been shown in placebo-controlled trials to delay the conversion of the clinically isolated syndrome to clinically definite disease, Dr. Miller and Dr. Leary wrote.

The PreCISE (Presenting With a Clinically Isolated Syndrome) study was funded by Teva Pharmaceutical Industries, which markets glatiramer acetate under the brand name Copaxone. Dr. Comi, along with several of his co-authors, acknowledged relationships with Teva. He served on company advisory boards, he served as a consultant, and he received honoraria for speaking activi-

**All patients in the trial had a single unifocal neurologic event less than 90 days earlier along with a brain MRI showing at least two cerebral lesions at least 6 mm in diameter.**

ties. In addition, Dr. Comi disclosed relationships with Novartis, Sanofi-Aventis, Merck-Serono, Biogen-Dompe, and Bayer Schering.

The trial involved 481 patients at 80 sites in 16 countries. They were randomized to receive either 20 mg per day of subcutaneous glatiramer acetate or placebo for up to 36 months.

Patients were 18-45 years old at trial entry. All had a single unifocal neurologic event less than 90 days earlier along with a brain MRI showing at least two cerebral lesions at least 6 mm in diameter. Patients were excluded if they had a multifocal clinical presentation, diseases other than MS responsible for the clinical or MRI presentation, or had used beta interferon, chronic corticosteroids, or any experimental or investigational drugs within 6 months of screening.

The most common adverse events among patients taking glatiramer acetate were injection-site reactions (56% vs. 24% for those taking placebo) and immediate postinjection reactions (19% vs. 5%).

Dr. Miller and Dr. Leary wrote that some neurologists are likely to recommend beta interferon or glatiramer acetate to most patients with a clinically isolated syndrome. Others, however, will choose to take a wait and see approach, reasoning that many of these patients will never progress and that others will remain well for a long time.

Dr. Miller reported that he has received research grants through his institution for companies that manufacture drugs for MS, and has also received honoraria and travel expenses from them. Dr. Leary also reported receiving travel grants for meetings from such companies, including Teva. ■

to the effect of either inhibitor given alone. Iloperidone doses should therefore be reduced by about one-half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor.

## 7.2 Potential for FANAPT to Affect Other Drugs

*In vitro* studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, or CYP2E1. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

**Dextromethorphan:** A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in  $C_{max}$  of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

**Fluoxetine:** A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

## 7.3 Drugs that Prolong the QT Interval

FANAPT should not be used with any other drugs that prolong the QT interval [see *Warnings and Precautions* (5.2)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

FANAPT caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m<sup>2</sup> basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m<sup>2</sup> basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m<sup>2</sup> basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

There are no adequate and well-controlled studies in pregnant women. FANAPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 8.2 Labor and Delivery

The effect of FANAPT on labor and delivery in humans is unknown.

### 8.3 Nursing Mothers

FANAPT was excreted in milk of rats during lactation. It is not known whether FANAPT or its metabolites are excreted in human milk. It is recommended that women receiving FANAPT should not breast feed.

### 8.4 Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

### 8.5 Geriatric Use

Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients.

Of the 3210 patients treated with FANAPT in pre-marketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia [see *Boxed Warning and Warnings and Precautions* (5.1)]. The safety and efficacy of FANAPT in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with FANAPT, vigilance should be exercised.

### 8.6 Renal Impairment

Because FANAPT is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of FANAPT. Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations ( $C_{max}$ ) of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 any of the three analytes measured.  $AUC_{0-\infty}$  was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

### 8.7 Hepatic Impairment

A study in mild and moderate liver impairment has not been conducted. FANAPT is not recommended for patients with hepatic impairment.

### 8.8 Smoking Status

Based on *in vitro* studies utilizing human liver enzymes, FANAPT is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

## 10 OVERDOSAGE

### 10.1 Human Experience

In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of FANAPT was documented in eight patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a three-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a four-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension) of FANAPT.

### 10.2 Management of Overdose

There is no specific antidote for FANAPT. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

## 16 STORAGE

Store FANAPT tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect FANAPT tablets from exposure to light and moisture.

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