

New MS Agent Reduces Relapse Rate, Disability

BY HEIDI SPLETE

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TORONTO — The investigational drug fingolimod at doses of 0.5 mg and 1.25 mg appears to be a safe and effective treatment for adults with multiple sclerosis, based on data from more than 1,000 patients.

In previous studies, fingolimod had “a clear cut effect on inflammatory outcomes” in relapsing-remitting multiple sclerosis patients, said Dr. Ludwig Kappos of University Hospital in Basel, Switzerland.

The current phase III study addressed whether the effects of fingolimod (FTY720) persisted over time, and whether a 0.5-mg dose is as effective as the previously studied 1.25-mg dose. The main outcome was relapse rate per year over a 2-year follow-up period.

The Food and Drug Administration is scheduled to review the safety and efficacy data for fingolimod this month.

The Fingolimod (FTY720) vs. Placebo in Relapsing-Remitting Multiple Sclerosis (FREEDOMS) study included 1,272 patients aged 18-55 years.

The average age of the patients was 37 years, and the average duration of MS was 8 years.

Patients with systemic or immune system disease were excluded, and 1,033 patients completed the study.

Patients were randomized to receive a daily dose of 1.25 mg fingolimod, 0.5 mg fingolimod, or a placebo.

The annualized relapse rate was reduced by 54% in patients who took 0.5 mg of fingolimod and by 60% in those who took 1.25 mg of fingolimod.

There was no significant difference in effectiveness between the doses, and both doses were significantly more effective than the placebo.

After 24 months, significantly more patients in either fingolimod group (70%-75%) were relapse free, compared with 46% of the placebo group.

In addition, both the 1.25-mg and 0.5-mg doses of fingolimod were associated with of 32% and 30%, reductions, respectively, in the risk of 3-month confirmed disability progression. Both reductions were significant, compared with placebo.

Similarly, both the 1.25-mg and 0.5-mg doses were associated with reductions in risk of 6-month confirmed disability progression of 40% and 37%,

also significant compared with placebo.

Safety and tolerability data for the study population were presented separately in a poster by Dr. Paul O'Connor of St. Michael's Hospital, Toronto, and his colleagues.

In the safety analysis, the researchers evaluated all patients at baseline screening, week 2, and months 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24.

Overall, the incidence of any adverse

event was 94% in both of the fingolimod groups and 93% in the placebo group. The incidence of an adverse event that caused a patient to stop treatment was 14% in the 1.25-mg group, and 8% in both the 0.5-mg and placebo groups.

Serious adverse events were reported in 51 patients (12%) in the 1.25-mg group, 42 patients (10%) in the 0.5-mg group, and 56 patients (13%) in the

People who have had chicken pox are at risk for shingles and postherpetic neuralgia (PHN) pain^{1,2}
This year, ~1 million Americans will develop shingles.^{1,2}
1 in 5 of them will go on to develop PHN pain¹



VITALS

Major Finding: The annualized relapse rate was reduced by 54% in multiple sclerosis patients who took 0.5 mg of fingolimod and by 60% in those who took 1.25 mg of fingolimod. After 24 months, around 70% of patients given fingolimod were relapse free, compared with 46% of the placebo group.

Data Source: A randomized, double-blind, placebo-controlled phase III study of 1,272 adults with MS.

Disclosures: The study was supported by Novartis Pharma AG. Dr. Kappos has received research support from multiple pharmaceutical companies, including Novartis. Dr. O'Connor has served as a consultant and received research support for multiple pharmaceutical companies, including Novartis.

Indication

LIDODERM (lidocaine patch 5%) is indicated for relief of pain associated with post-herpetic neuralgia. Apply only to **intact skin**.

Important Safety Information

LIDODERM is contraindicated in patients with a history of sensitivity to local anesthetics (amide type) or any product component.

Even a *used* LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important to **store and dispose of LIDODERM out of the reach of children, pets, and others**.

Excessive dosing, such as applying LIDODERM to larger areas or for longer than the recommended wearing time, could result in increased absorption of lidocaine and high blood concentrations leading to serious adverse effects.

Avoid contact of LIDODERM with the eye. If contact occurs, immediately wash the eye with water or saline and protect it until sensation returns.

Avoid the use of external heat sources as this has not been evaluated and may increase plasma lidocaine levels.

Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally. LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic. LIDODERM should also be used with caution in pregnant (including labor and delivery) or nursing mothers.

Allergic reactions, although rare, can occur.

During or immediately after LIDODERM treatment, the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours. Other reactions may include dizziness, headache, and nausea.

When LIDODERM is used concomitantly with local anesthetic products, the amount absorbed from all formulations must be considered.

placebo group. Serious adverse events included cardiovascular disorders, neoplasms, nervous system disorders, macular edema, and abnormal liver function test results.

Sinus bradycardia, the most common ECG finding, occurred in 47 patients (11%) in the 1.25-mg group, 20 patients (5%) in the 0.5-mg group, and 6 patients (2%) in the placebo group.

In addition, first- and second-degree atrioventricular blocks were reported in 20 patients (5%) and 1 patient (0.2%), respectively, in the 0.5-mg group, compared with 37 patients (9%) and 4 pa-

tients (1%), respectively, in the 1.25-mg group.

Malignant neoplasms were reported in 4 patients in each of the fingolimod groups and in 10 patients in the placebo group.

All 11 cases of skin cancer reported in the study were successfully treated with excision.

Abnormal liver function tests were reported more than twice as frequently in the fingolimod 1.25-mg and 0.5-mg groups, compared with placebo (19%, 16%, and 5%, respectively).

But "liver enzyme elevations were

asymptomatic and improved once therapy was discontinued; no patient developed liver failure," the investigators wrote.

In the 1.25-mg group, one case of ischemic stroke occurred during the study period, and a transient ischemic attack occurred 8 months after the discontinuation of treatment.

No clinically relevant pulmonary function changes were observed in any of the groups.

All seven reported cases of macular edema occurred in the group that took 1.25 mg of fingolimod, and all cases re-

solved after treatment was discontinued.

The overall incidence of infections was similar (69%-72%) for all three groups, and included herpesvirus infections, lower respiratory tract infections, and urinary tract infections.

The results support safety data from previous studies and suggest that most patients with MS tolerate oral fingolimod, the researchers said.

Also consistent with previous studies, "the overall safety profile of fingolimod 0.5 mg appears to be more favorable than that of the 1.25-mg dose," they added. ■

For the many places patients may experience PHN pain LIDODERM® fits

Proven efficacy in 2 randomized, placebo-controlled clinical trials³⁻⁶

- In a 12-hour study, patients experienced pain relief at 30 minutes after the first dose vs observation cohort ($P=0.0001$; $N=35$)^{4,a}
 - Significant reduction in pain intensity vs placebo at hours 4-12 ($P<0.001$ to $P=0.038$)
- In a 2-week study, 84% of patients had moderate to complete pain relief at 2 weeks vs placebo ($P<0.001$; $N=32$)^{5,b,c}

Favorable safety profile³

- Nonnarcotic, nonsedating, nonscheduled
- May be used in patients who have comorbidities or are taking concomitant medications

Immediately discard used patches or remaining unused portions of cut patches in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

Before prescribing LIDODERM, please refer to the accompanying brief summary of full Prescribing Information.

^a A randomized, double-blind, placebo-controlled, 4-way crossover trial ($N=35$) assessed safety and efficacy of LIDODERM. Patients were allodynic with a mean age of 75 years and mean PHN duration of 48 months. Pain intensity measured with horizontal 100-mm Visual Analogue Scale: 0=no pain and 100=worst pain imaginable. Measurements were recorded before patch application, at 30 minutes, and hours 1, 2, 4, 6, 9, and 12. Least-squares means were used as the best unbiased estimate of patients' mean values.

^b Demonstrated over 14 days in a post hoc analysis of a randomized, enriched-enrollment, double-blind, placebo-controlled, crossover trial. Patients enrolled in the study had been using LIDODERM for ≥ 1 month (ie, enriched enrollment); mean age of 77.4 years and mean PHN duration of 7.3 years. Pain relief measured using 6-item verbal scale: 0 (worse), 1 (no relief), 2 (slight relief), 3 (moderate relief), 4 (a lot of relief), and 5 (complete relief). Patients exited the study if their verbal pain relief rating decreased more than 2 categories for any 2 consecutive days from baseline.

^c Results of enriched-enrollment studies can't be generalized to the entire population; subjects in such studies may be able to distinguish the active drug from placebo based on nontherapeutic features of the treatments.

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