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Levotofisopam: A Novel Homophthalazine with Potential for Treatment of Stress-Related Disorders

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Introduction: Levotofisopam is the S-enantiomer of racemic tofisopam, a homophthalazine prescribed outside the United States for such stress-related disorders as anxiety, functional gastrointestinal disorders, and symptoms of menopause. Thought to affect autonomic tone via interaction with subcortical 2,3-benzodiazepine receptors, levotofisopam has shown promise in animal models of stress-related gastrointestinal dysfunction and menopause. We conducted a trial of levotofisopam in healthy human volunteers.

Methods: The safety, tolerability, and pharmacokinetics of ascending single doses of levotofisopam were examined in a randomized, double-blind, placebo-controlled trial in healthy human volunteers. A total of 42 subjects were randomized to receive single doses of levotofisopam (50 mg, 100 mg, 200 mg, 300 mg, or 400 mg; n = 6/dose) or placebo (n = 12).

Results: Levotofisopam was generally well tolerated up to the highest dose level (400 mg). The incidences of treatment-emergent adverse events (TEAEs) were similar for levotofisopam (40%) and placebo (50%). All TEAEs in levotofisopam-treated subjects were mild, and there were no clear drug or dose relationships for any TEAE. No serious or severe TEAEs occurred during the study, no subjects discontinued the study prematurely due to TEAEs, and no concomitant medications were required for treatment of any TEAE.

Levotofisopam reached C_{max} approximately 1 hour after administration at all doses, with mean C_{max} ranging from 64 to 1201 ng/mL and mean AUC from 87 to 2924 ng·hr/mL. The mean half-life of levotofisopam appeared to lengthen as the dose increased, from 1.4 hours at 50 mg to 8.1 hours at 400 mg. The disproportionate increases in C_{max} and AUC relative to increasing dose suggest that the bioavailability of levotofisopam may be somewhat dose-dependent.

Conclusions: Levotofisopam appears to be well tolerated at single doses of up to 400 mg in healthy volunteers. This finding, combined with robust responses in preclinical studies, support further clinical study of levotofisopam in the treatment of stress-related conditions, such as anxiety and the symptoms of menopause. A multiple-dose study of the effects of levotofisopam in healthy men and menopausal women is currently underway.

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