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# HerbClip™



**File: ■ Lavender (*Lavandula angustifolia*)**
**■ Silexan®**
**■ Cytochrome P450 (CYP)**

**HC 041355-480**

**Date: September 13, 2013**

**RE: Oral Lavender Essential Oil Preparation Does Not Affect Cytochrome P450 (CYP) Enzymes**

Doroshyenko O, Rokitta D, Zadoyan G, et al. Drug cocktail interaction study on the effect of the orally administered lavender oil preparation Silexan on cytochrome P-450 enzymes in healthy volunteers. *Drug Metab Dispos*. 2013;41(5):987-993.

Assessing the effect of new therapeutics on pharmacokinetic processes that may result in drug-drug interactions is an integral part of drug development. The purpose of this randomized, double-blind, placebo-controlled, crossover study was to evaluate the effects of Silexan® on the activity of 5 major cytochrome P450 (CYP) enzymes. Silexan (the active substance of Lasea®; W. Spitzner Arzneimittelfabrik GmbH [part of Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany]; Ettlingen, Germany) is an oral preparation of lavender (*Lavandula angustifolia*) flower steam-distilled essential oil that has been approved in Germany for the treatment of restlessness with anxious mood. Silexan complies with the lavender oil monograph of the European Pharmacopoeia with respect to all quality parameters, including the required contents of 20-45% and 25-46% linalool and linalyl acetate, respectively.

The trial was conducted in compliance with the 2012 guidelines of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the investigation of drug interactions; it employed a crossover design with well-controlled conditions, including supervised intake of the study drug, a clinically relevant dose of the drug, proof of exposure, and standardized food and fluid intake for assessment of enzyme activity. Healthy Caucasian men and women (n = 17; aged 18-55 years) participated in this German study (location not reported). At the eligibility assessment, blood was drawn for genotyping, and individuals with nonfunctional alleles of CYP2C19 and CYP2D6 were excluded. To maximize exposure and therefore increase the chance of detecting potential interactions, the administered dose of Silexan was twice the clinical norm.

Subjects received either placebo or a 160-mg Silexan softgel capsule once daily for 11 days. On day 11, subjects also received a 5-probe phenotyping cocktail that contained 150 mg of caffeine to evaluate CYP1A2, 125 mg of tolbutamide to evaluate CYP2C9, 30

mg of dextromethorphan HBr to evaluate CYP2D6, 2 mg of midazolam to evaluate CYP3A4, and 20 mg of omeprazole to evaluate CYP2C19. [Note: The EMA considers omeprazole as not sufficiently validated as a phenotyping drug, but accepts its use as a "standard of convenience" in the absence of better choices.] There was a 21-day washout period between the crossover treatments. One week prior to commencement and throughout the study, subjects were prohibited from consuming alcohol, grapefruit (*Citrus* × *paradisi*) products, and quinine (*Cinchona* spp.) products.

Subjects fasted 9 h before and 6 h after the drug cocktail administration, and fluid intake was also regulated. Blood was drawn on days 5, 10, and 11 prior to dosing. On day 11, blood was drawn 10, 20, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 h post-dose. Silexan treatment compliance was confirmed by analyzing linalool concentrations in the blood samples; these assays also confirmed that steady-state plasma levels of Silexan were reached by day 11.

One subject withdrew after completing the first arm of the study due to adverse events (AEs; nausea and vomiting); 16 subjects completed the trial. One subject was identified as a poor metabolizer of CYP2D6 substrates and hence was excluded from the CYP2D6 analysis.

For CYP1A2, CYP2C9, CYP2D6, and CYP3A4, the 90% confidence intervals (CIs) for the ratios of Silexan to placebo were within the predefined acceptance range of 0.70-1.43, indicating that there were no pharmacokinetic interactions. For CYP2C19, the 90% CI was above the upper threshold. However, as there was marked heterogeneity between subjects, this result may only reflect the high variability in omeprazole pharmacokinetics and may not be indicative of a clinically relevant interaction between Silexan and CYP2C19 substrates.

Mild eructation (burping) was the most frequently reported AE associated with Silexan treatment, occurring in 58.8% of subjects. There was also 1 case of diarrhea and 1 case of nausea that was considered possibly related to Silexan. There were no serious AEs. There were no clinically relevant changes in vital signs, electrocardiograms (ECGs), or laboratory parameters.

The authors conclude that repeated administration of 160 mg/day of oral Silexan had no clinically relevant inhibitory or inducing effects on CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 enzymes, even at dosages that were twice the clinical norm. An inhibitory action of Silexan on CYP2C19 cannot be excluded because statistically the number of subjects was too small to rule out intrasubject variability as a causal factor; the CYP2C19 study should be replicated with additional subjects.

*—Heather S. Oliff, PhD*

Referenced article can be found at http://intl-dmd.aspetjournals.org/content/early/2013/02/11/dmd.112.050203.full.pdf+html.