



New Extended-Release Minocycline: First Systemic Antibiotic Approved for the Treatment of Acne

Supported by a restricted educational grant from Medicis Pharmaceutical Corporation.

Introduction

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Key Bioavailability Features of a New Extended-Release Formulation of Minocycline Hydrochloride Tablets

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For a long time, minocycline has been recognized as highly efficacious for the treatment of acne vulgaris but with use-limiting acute vestibular adverse events (AVAEs). Based on the concept that lowered overall systemic exposure to minocycline should reduce unwanted side effects, a program was initiated to develop a modified-release formulation for clinical testing. An extended-release (ER) minocycline hydrochloride tablet formulation was developed that demonstrated delayed time of maximum concentration (t_{max} , 3½–4 hours) compared with a nonmodified-release minocycline (t_{max} , 2¼–3 hours), and a lower maximum concentration of drug (c_{max}) in the blood (90%) compared with nonmodified-release formulations. At steady state (day 6), the ER-minocycline formulation had a 0- to 24-hour area under the curve (AUC_{0-24}) and c_{max} of 33.32 $\mu\text{g}\times\text{h}/\text{mL}$ and 2.63 $\mu\text{g}/\text{mL}$, respectively, compared with

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46.35 $\mu\text{g}\times\text{h}/\text{mL}$ and 2.92 $\mu\text{g}/\text{mL}$, respectively, for the nonmodified-release minocycline. These studies demonstrated that the new ER-minocycline hydrochloride formulation is not bioequivalent to the immediate-release (IR) minocycline hydrochloride formulation currently on the market. The favorable pharmacokinetic profile of ER minocycline also was not affected by concomitantly ingested food, including dairy products.

Dose-Ranging Efficacy of New Once-Daily Extended-Release Minocycline for Acne Vulgaris

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Daniel M. Stewart, DO; Helen Mary Torok, MD; Jonathan S. Weiss, MD; R. Todd Plott, MD; for the Solodyn Phase 2 Study Group

A multicenter, 12-week, randomized, double-blinded, placebo-controlled, dose-ranging study was conducted in 233 subjects with moderate to severe facial acne vulgaris to determine the lowest effective once-daily oral dose of a new extended-release (ER) minocycline hydrochloride formulation with the safest adverse effect profile. Subjects randomly were assigned to treatment with daily dosages of ER-minocycline 1-, 2-, or 3-mg/kg tablets, or daily placebo tablets, for 84 days. At the end of the 12 weeks, the number of inflammatory lesions decreased approximately 50% from baseline levels in the dose groups. No dose-dependent effect was observed, with the percentage decrease in the number of inflammatory lesions in the 1-mg/kg treatment group being equal to or greater than higher doses. The pairwise difference between the ER-minocycline 1 mg/kg and placebo groups in the percentage decrease in inflammatory lesions was statistically significant ($P=.015$). Acute vestibular adverse events (AVAEs) appeared to be dose proportional, with the incidence being similar in the lowest (1 mg/kg) dosing group (24%) and in the placebo group (26%). Higher-dose regimens were associated with a higher incidence of central nervous system side effects and AVAEs. A 1-mg/kg daily dosage of the new ER-minocycline formulation is the lowest effective dose with the safest side effect profile, with higher-dose regimens offering no substantial therapeutic advantages.

Safety and Efficacy of a New Extended-Release Formulation of Minocycline

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The complete safety and efficacy of a new extended-release (ER) minocycline hydrochloride formulation were assessed in an analysis of a phase 2 dose-finding study and 2 phase 3 safety and efficacy studies. The studies were similar in design, subject populations, and shared common dose groups of subjects given ER minocycline 1 mg/kg daily or placebo over 12 weeks. The similar designs were prospective, multicenter, randomized, double-blinded, and placebo-controlled. A total of 1038 subjects with moderate to severe acne were available for the pooled analysis. Independently, each study showed that treatment with ER-minocycline significantly reduced ($P<.001$) the number of inflammatory lesions and significantly improved ($P<.001$) their Evaluator's Global Severity Assessment (EGSA) scores (phase 3 studies). Analysis of the pooled population confirmed the results of the individual studies. The percentage of subjects reporting acute vestibular adverse events (AVAEs) was comparable between those receiving the ER-minocycline 1-mg/kg dose and placebo (approximately 10% of subjects in each group) for both the individual studies and the pooled population. It was concluded that a novel ER-minocycline formulation that delivers consistent levels of drug at a 1-mg/kg dose reduces dose-dependent AVAEs while reducing inflammatory lesions and improving the overall appearance of patients with acne vulgaris.