



## DERMATOLOGY EXPRESS REPORT™ FAX

### Weight-based Dosing of a Novel Antibiotic for Moderate-to-Severe Acne Vulgaris Offers Potential for Improved Safety and Tolerability

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#### Expert Commentary

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The recent approval of minocycline extended-release tablets (Solodyn) by the Food and Drug Administration (FDA) offers a major advancement for treating moderate-to-severe acne vulgaris. Minocycline extended-release tablets were formulated to provide optimal efficacy in treating moderate-to-severe acne vulgaris, while potentially minimizing the vestibular adverse effects that have been associated with minocycline administration.<sup>1</sup> Unlike immediate-release minocycline formulations, minocycline extended-release tablets offer a unique pharmacokinetic delivery that, when dosed on a 1 mg/kg weight-basis,<sup>2</sup> provides the lowest effective dose of minocycline for treating moderate-to-severe acne vulgaris. In addition, minocycline extended-release tablets are administered once daily, thus offering the potential to enhance patient compliance. Minocycline extended-release tablets are indicated for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris and represent the first oral systemic antibiotic approved by the FDA as first-line therapy for the treatment of acne.<sup>2</sup>

Systemic antibiotic therapy is indicated in the treatment of moderate-to-severe inflammatory acne, or acne considered emotionally burdensome for the patient for psychological or social reasons.<sup>3</sup> Physicians have used erythromycin, tetracycline, doxycycline, and minocycline to treat acne vulgaris for decades. However, until recently, these antibiotics had not been evaluated in pivotal phase 3 clinical studies for the systemic treatment of acne. Erythromycin therapy may be associated with intolerable gastrointestinal side effects including nausea, vomiting, diarrhea, abdominal pain, and anorexia.<sup>3</sup> Tetracycline should be administered

on an empty stomach as the presence of food or dairy products may hinder its absorption. Consequently, tetracycline may be associated with minor gastrointestinal side effects including nausea, vomiting, and diarrhea. Doxycycline and minocycline are absorbed well, and minocycline is less likely than erythromycin and tetracycline to produce gastrointestinal side effects.<sup>4</sup> However, doxycycline may be limited by dose-related phototoxicity in some patients,<sup>5</sup> and minocycline may be associated with vestibular adverse events and tissue pigmentation.<sup>6</sup> Vestibular adverse events are the most common reason for treatment discontinuation of minocycline.<sup>7,8</sup>

The clinical development of minocycline extended-release tablets was based on 2 proposed hypotheses: first, that the efficacy of minocycline in treating acne vulgaris was not related to its serum concentrations; and second, that the high peak serum concentrations of minocycline were responsible for the acute vestibular adverse events. The highly lipophilic property of minocycline is well-suited for penetration into lipid-rich tissues such as the pilosebaceous unit,<sup>9</sup> where sebum serves as a growth medium for *Propionibacterium acnes* (*P. acnes*) within the follicles. The extent of systemic minocycline bioavailability in acne is less important than the lipophilic property of the molecule, as accumulation of greater minocycline levels in the pilosebaceous unit is believed to provide a clinically effective level of *P. acnes* reduction.<sup>10</sup> The pharmacokinetic delivery of minocycline extended-release tablets avoids the more rapid increase in serum levels observed with immediate-release minocycline. A more rapid increase in the serum level of minocycline may influence the potential for vestibular adverse events (eg, dizziness, vertigo).<sup>10</sup> Minocycline extended-release tablets were designed to address the clinical conundrum of finding an effective dose for treating moderate-to-severe acne vulgaris based on patient weight while minimizing potential adverse events.

This *Dermatology Express Report™ Fax* reviews the safety and tolerability profiles of minocycline extended-release tablets. An in-depth *Dermatology Express Report™* will review the safety and efficacy of minocycline extended-release tablets and will be distributed in the near future.

## Minocycline Extended-release Tablets— Safety and Tolerability

The safety and tolerability of once-daily minocycline extended-release tablets were evaluated in 2 multicenter, randomized, double-blind, placebo-controlled, 12-week phase 3 studies.<sup>2</sup> A total of 924 subjects (age ≥12 years) with non-nodular, moderate-to-severe inflammatory acne vulgaris were randomized to 1 mg/kg minocycline extended-release tablets or placebo for 12 weeks. Safety assessments were based on the incidence of adverse events and clinical laboratory parameters (complete blood counts, serum chemistries).

At the end of 12 weeks, minocycline extended-release tablets were well-tolerated with overall treatment-emergent adverse events comparable to placebo (Table 1). The majority of adverse events were mild in severity. In terms of adverse events possibly related to vestibular function (eg, nausea, dizziness, vomiting, tinnitus), the incidence of vestibular adverse events was comparable between minocycline extended-release tablets and placebo.

**Table 1. Selected Treatment-emergent Adverse Events in at Least 2% of Clinical Trial Subjects.**

	Minocycline Extended-release (1 mg/kg) (n = 674)	Placebo (n = 364)
At least one treatment-emergent adverse event	379 (56.2%)	197 (54.1%)
Headache	152 (22.6%)	83 (22.8%)
Nausea	64 (9.5%)	41 (11.3%)
Fatigue	62 (9.2%)	24 (6.6%)
Dizziness	59 (8.8%)	17 (4.7%)
Diarrhea	35 (5.2%)	21 (5.8%)
Gastrointestinal pain	34 (5.0%)	25 (6.9%)
Pruritus	31 (4.6%)	16 (4.4%)
Malaise	26 (3.9%)	9 (2.5%)
Abdominal pain, upper	22 (3.3%)	14 (3.8%)
Mood alteration	17 (2.5%)	9 (2.5%)
Vomiting	14 (2.1%)	9 (2.5%)
Somnolence	13 (1.9%)	3 (0.8%)
Urticaria	10 (1.5%)	1 (0.2%)
Tinnitus	10 (1.5%)	5 (1.4%)

An analysis of treatment-emergent adverse events by age group revealed no significant differences between pediatric subjects (12 to 17 years) and adult subjects (≥18 years). No clinically significant treatment-dependent effects on clinical laboratory parameters associated with hepatic or thyroid function were observed.

Adverse events led to treatment discontinuation in 20 subjects (3.0%) treated with minocycline extended-release tablets compared with 6 subjects (1.6%) treated with placebo. The most common reasons for treatment discontinuation due to adverse events were pruritus, urticaria, rash, and fatigue.

During clinical studies of minocycline extended-release tablets, higher dose regimens (2 mg/kg, 3 mg/kg) were associated with an increased risk of vestibular adverse events and offered no additional therapeutic benefit.<sup>2</sup> The results of these studies suggest that minocycline extended-release tablets offer a unique pharmacokinetic delivery that, when dosed on a 1 mg/kg weight-basis, is well-tolerated with adverse events comparable to placebo.

## Conclusion

Minocycline extended-release tablets were formulated to provide optimal efficacy in treating moderate-to-severe acne vulgaris while potentially minimizing the vestibular adverse effects that have been associated with minocycline administration, primarily with use of higher doses. Unlike immediate-release minocycline formulations, minocycline extended-release tablets offer a unique pharmacokinetic delivery that, when dosed on a 1 mg/kg weight-basis, provides the lowest effective dose for treating moderate-to-severe acne vulgaris. In addition, minocycline extended-release tablets are administered once daily, thus offering the potential to enhance patient compliance. Future head-to-head comparative clinical trials of minocycline extended-release tablets are planned to assess fully its potential benefits against other minocycline formulations.

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