

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-444/S-036

50-445/S-019

50-649/S-011

MEDICAL REVIEW

Medical Officer's Review of Geriatric Labeling Supplements

1.0 Identifying Information

1.1 NDA : 50-445/SLR-019 (Minocin® Oral suspension)
50-649/SLR-011 (Minocin® Pellet Filled Capsules)
50-444/SLR-036 (Minocin® Intravenous)

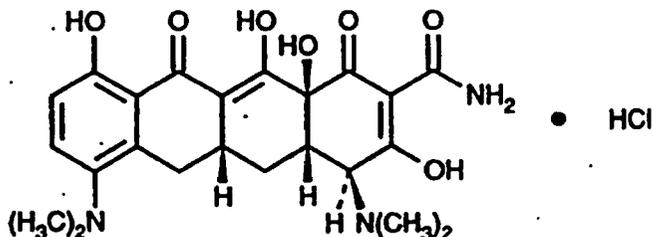
1.2 Applicant: Wyeth-Ayerst Laboratories
150 B/3 North Radnor-Chester Road
St. Davids, PA 19087
Contact Person: Patricia Kuker Staub, RPh, JD
Associate Director II
Worldwide Regulatory Affairs

1.3 Submission/Review Dates:
Date of Submission: August 11, 1999
Dates Received by CDER: August 11, 1999
Date Reassigned to MO: March 15, 2002
Date 1st draft Review Completed: April 15, 2002
Date Final Review Completed: May 28, 2002

1.4 Drug Identification:

Proprietary Name: MINOCIN®
Generic Name: Minocycline Hydrochloride
Dosage Form: Oral solution; pellet-filled capsules; and solution for Intravenous Injection
Route of Administration: Oral and Intravenous
Category: Semisynthetic derivative of tetracycline
Chemical Name: 4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride

Chemical structure:



Molecular weight: 493.94

Molecular formula: $C_{23}H_{27}N_3O_7 \cdot HCl$

2.0 Materials reviewed: A total of ten volumes were originally submitted by the applicant. A new volume (Amendment to the three NDA labeling supplements) was submitted on March 26, 2002 in response to the Division's (DAIDP) request for the sodium and potassium content in the individual Minocin drug substances and products.

- Applicant's Cover Letter
- Completed Form FDA 356h
- Completed Form FDA 3397
- Table of Contents; One copy of Draft Labeling; One copy of the Medical Literature Search Document Supporting the Draft Labeling; Review of Adverse Events; One copy of the September 4, 1998 Approvable Letter for Supplements 029, 033, and 034.

MO Comment: *The review of the three labeling supplements (NDA 50-445/S019, 50-649/S-011 and 50-444/S-036) is integrated since the proposed Geriatric use labeling revisions for the current insert are identical and apply to these three applications. The differences between the three applications is in the dosage form and administration.*

3.0 Purpose of Application:

The purpose of these supplemental New Drug Applications is to revise the labeling for MINOCIN® (oral suspension, pellet-filled capsules and intravenous injection) which will provide geriatric labeling for MINOCIN®, in accordance with the Final Rule published in the Code of Federal Register notice of August 27, 1997, entitled " Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection of the Labeling, vol 62, No.166.

4.0 Background

The applicant submitted the following applications (NDA 50-445/S-019, 50-649/S-011 and 50-444/S036) for Minocin drug products including Minocin® Oral Suspension, Minocin® Pellet-Filled Capsules and Minocin® Intravenous for geriatric use in accordance to the Final Rule published in the Federal Register amending CFR 201.57. The proposed labeling text under the PRECAUTIONS section, is as follows:

“Geriatric use: Clinical studies of [oral minocycline or intravenous minocycline] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see WARNINGS, DOSAGE AND ADMINISTRATION).

Data Submitted in Support of the Geriatric Use Label:

In support of the proposed geriatric labeling, the applicant performed a literature search for use of minocycline in the elderly. EMBASE was utilized for the search, from the period between 1988 to December 1998, for patients of all ages. Out of the 1390 articles searched, 152 articles contained information on patients < 65 and >65 years. Medline was also utilized as a search tool by the applicant; 843 articles were found and 119 articles provided information comparing elderly and non-elderly patients.

The applicant conducted a search of their Global Safety Surveillance and Epidemiology database to identify reports of adverse drug experiences associated with the use of the Minocin “family” products in patients 65 to 75 years of age, and ≥75 years of age. The database contains reports received from health professionals, consumers, clinical studies, and published literature. According to the applicant, their review identified no information indicating differences in safety or effectiveness in geriatric populations.

Summaries of published clinical studies including patients over the age of 65 years:

- Tilley BC, Alarcon GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA, et al: Minocycline in rheumatoid arthritis: a 48-week, double blind, placebo-controlled trial. *Ann Intern Med* 1995; 122(2):81-9.

A double-blind, randomized, multicenter, 48-week trial of oral minocycline or placebo was performed to assess the safety and efficacy of minocycline in the treatment of rheumatoid arthritis. Patients consisted of 219 adults with active rheumatoid arthritis who had previous

limited treatment with disease-modifying drugs. One-hundred nine and 110 patients were randomly assigned to receive oral minocycline 200 mg/day and placebo, respectively. The primary outcome measures included improvement in joint swelling and improvement in joint tenderness. The mean ages \pm SD were as follows: 1) minocycline group, 55.0 ± 12.8 ; and 2) 53.5 ± 13.5 in the placebo group. Thirty-nine percent of the minocycline group and 34% of the placebo group reported dizziness. Elevated liver function test results were reported for two patients in the minocycline group and three patients in the placebo group. Two patients receiving minocycline had total bilirubin levels greater than 1.5 mg/dL ($25.65 \mu\text{mol/L}$) during the study. One patient in the minocycline group and one patient in the placebo group had elevated creatinine levels during the study. The frequency of reported side effects was similar in both groups, and no serious toxicity occurred. The study concluded that minocycline is safe and effective for patients with mild to moderate rheumatoid arthritis.

Note: The article did not provide the particular study results in geriatric patients, 65 years old and over.

- **Gardezi SAR, Chaudhry AM, Sial GAK, Ahmad I, Yousuf A: Minocycline HCl in urinary tract infection-a clinical trial. *JPMA* 1983;33(12):294-8.**

Minocycline HCl was tried in 100 patients with urinary tract infections; 17 patients were 61 to 68 years old. Sixty-five patients were selected from the surgical unit, 20 from the outpatient department and 15 from the emergency room in Mayo Hospital, Lahore. Group A consisted of 50 patients who underwent a surgical procedure. The remaining 50 patients in Group B were treated conservatively. Initial dose of 200 mg of Minocycline HCl was followed by 100 mg twice daily for 5-7 days in Group A and 10-15 days in group B depending upon the response in individual cases. The adverse reactions noted in the study included loose motions in 4 patients; ulcers in the mouth, 3 patients; vomiting in 3 patients; and dizziness and light headache in 3 patients. The study concluded that minocycline HCl was highly effective in patients with *Escherichia Coli* and *Enterococcus faecalis* infections.

- **O'Dell JR, Haire CE, Palmer W, Drymalski W, Wees S, Blakely K, et al: Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized, double-blind, placebo-controlled trial. *Arthritis and Rheumatism* 1997;40(5):842-8.**

The Rheumatoid Arthritis Investigational network enrolled 46 patients with rheumatoid arthritis (RA) of <1 year duration into a 6-month randomized, double-blind, placebo-controlled study of minocycline 100 mg twice daily. All patients were rheumatoid factor positive. The objective of the study was to determine if minocycline is an effective therapy for seropositive rheumatoid arthritis when used within the first year of the disease. The primary endpoint of the study was successful completion of 6 months of treatment with no drug toxicity and maintaining 50% improvement in composite symptoms of RA. The mean ages (range) of patients were as follows: 41 (21-56) years in the minocycline group and 49

(28-70) years in the placebo group. Fifteen of 23 patients treated with minocycline and 3 of 23 patients treated with placebo met 50% improvement criteria at 3 months, and maintained at least a 50% improvement for 6 months with no significant drug toxicity. The article stated that one patient in the placebo group stopped treatment because of a gastrointestinal bleed. None of the minocycline-treated patients withdrew medication due to drug toxicity. The investigators concluded that patients with early seropositive RA, treatment with minocycline is superior to placebo.

Note: The study did not provide information in geriatric patients (65 years old and over) treated with minocycline.

- **Boivin JM, Issartel G, Zannad F: Double-blind, randomized, parallel group of minocycline 100 mg vs roxithromycin 300 mg for the treatment of acute bronchitis. *Therapie* 1995; 50:35-40.**

One-hundred twenty-four patients were enrolled in a randomized, parallel and double-blind study conducted in Nancy, France comparing the efficacy and tolerance of two drugs: roxithromycin 300 mg per day, and minocycline 100 mg per day in the treatment of adult acute bronchitis. The age range in the minocycline treatment group was 17 to 80 years; and 19 to 73 years of age in the roxithromycin treatment group. The adverse reactions reported in the study were as follows: headache (7.1%), giddiness (14.3%), nausea (7.1%) stomach ache (7.1%); diarrhea (17.9%) in the minocycline treated patients. In the roxithromycin treated patients, giddiness (8.7%); nausea (4.4%); stomach ache (8.7%); diarrhea (13%); and dysphagia (13%). The study concluded that clinical tolerance was estimated to be excellent in the two treatment groups.

Note: The article did not state the number of geriatric patients, 65 years old and over, who received minocycline therapy.

5.0 Proposed Labeling

5.1 The applicant's proposed label for Minocin contains the following new Geriatric Use subsection:

Geriatric use: Clinical studies of minocycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **WARNINGS, DOSAGE AND ADMINISTRATION**).

5.2 Medical Officer's Proposed Label for Minocin:

The Division of Anti-infective Drug Products (HFD-520) is suggesting the inclusion of the sodium content of antimicrobial agents in its geriatric use labeling supplements.

The information submitted by the applicant and reviewed by FDA chemist revealed that only Minocin oral suspension contains sodium. Minocin® IV and Minocin® pellet-filled capsules do not contain sodium in its formulations. The amount of Na⁺ is small and unlikely to have serious clinical consequences but should be stated in the label.

The labeling changes as proposed by the applicant are acceptable. In addition the following changes are also recommended by the reviewer regarding the sodium content in Minocin dosage forms: (Note: The recommended changes are underlined by the reviewer.)

The following statement should be added to the end of the Geriatric use subsection for NDA 50-445/SLR-019:

Minocin® Oral suspension contains 4.3 mg (0.18 mEq) of sodium per 5 mL.

The following statement should be added to the end of the Geriatric use subsection for NDA 50-649/SLR-011:

Minocin® Pellet-Filled Capsules (50 mg, 75 mg and 100 mg) do not contain sodium.

The following statement should be added to the end of the Geriatric use subsection for NDA 50-444/SLR-036:

Minocin® IV (sterile Minocycline Hydrochloride, USP) does not contain sodium.

6.0 Conclusion

It is recommended that the "Geriatric Use" Labeling Supplements for NDA 50-445/S-019; NDA 50-649/S-011; and NDA 50-444/S-036 be approved with the above recommendations added.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Alma Davidson
5/29/02 05:30:49 PM
MEDICAL OFFICER

John Alexander
5/31/02 02:28:13 PM
MEDICAL OFFICER

Janice Soreth
5/31/02 04:52:52 PM
MEDICAL OFFICER