CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-786

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA: 50-786
Review Number: 1
Date of Submission: 4/18/02 (Initially 9/28/01 as NDA 21-362)
Information to Sponsor: Yes ( ) No (X)

Sponsor: Axcan Scandipharm, Inc.
22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

Agent: CanReg, Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Manufacturer of Drug Substances:
1) Biskalcitrate potassium –
2) Metronidazole –
3) Tetracycline HCl –

Reviewer: Stephen G. Hundley, Ph.D., D.A.B.T.
Pharmacology/Toxicology Reviewer

Division: Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 8/7/02

Drug Product: Helicide®
New Molecular Entity: Biskalcitrate potassium
Generic Name: Not Applicable
Code Name: Not Applicable
Drug Substances: 1) Biskalcitrate potassium; CAS # -- None
2) Metronidazole; CAS # -- 443-48-1
3) Tetracycline HCl; CAS # -- 60-54-8
Molecular Weights: 1) Biskalcitrate potassium –
2) Metronidazole – 711.15
3) Tetracycline – 480.9
Molecular Formula: Biskalcitrate potassium –
NME Structure: Biskalcitrate potassium not structurally defined

Relevant IND:

Drug Class: Mucosal Protectant (Biskalcitrate potassium) and Antibiotic (Metronidazole and Tetracycline)

Indication: Eradication of *Helicobacter pylori*

Clinical Formulation: Single Triple Capsule containing 140 mg Biskalcitrate potassium, 125 mg Metronidazole, and 125 mg Tetracycline (tablet)

Route of Administration: Oral

Proposed Use: Three Single Triple Capsules of Helicide® to be taken orally four times daily for a period of 10 days in conjunction with a 20 mg Prilosec® (omeprazole) capsule taken twice daily over the same 10-day period.

Executive Summary

Recommendations:

Approvability – The NDA submission is approvable from the perspective of nonclinical pharmacology and toxicology.

Nonclinical Studies – Nonclinical studies are not required.

Labeling – The sponsor's proposed label is acceptable with regard to the nonclinical pharmacology and toxicology portions of the label.

Summary of Nonclinical Findings:

Nonclinical Overview – The sponsor did not conduct nonclinical studies in support of the IND and NDA submissions. Metronidazole, and tetracycline are approved drug products. The proposed daily dose levels of 1,500 mg metronidazole and 1,500 mg tetracycline are approved therapeutic levels. The dosing duration of 10 days is within the approved duration of dosing for each of these drugs. Therefore, nonclinical studies were not needed for metronidazole and tetracycline.

Biskalcitrate potassium is similar to colloidal bismuth subcitrate (CBS) also referred to as tripotassium dicitrato bismuthate which is the active ingredient in De-Noltab, an approved drug product in Europe. Current accepted therapeutic daily doses of CBS in Europe deliver approximately 480 mg equivalents of Bi_2O_3 daily for up to 8 weeks. The proposed daily biskalcitrate potassium dose level expressed as mg equivalents of Bi_2O_3 is approximately 480 mg (40 mg equivalents × 3 tablets × 4 daily doses). Any potential human toxicity from biskalcitrate potassium would be from excessive systemic levels of bismuth, particularly in the brain and central nervous system. There are, however, no indications of bismuth toxicity resulting from CBS therapy due in part to the low bioavailability (less than 1% following oral administration) and the relatively low dose

level compared to the amount of bismuth salt associated with human bismuth encephalopathy (10 g or more of bismuth nitrate daily for several months).

A synopsis of preclinical animal toxicology data supplied by the sponsor indicated that no adverse effects were observed in rats and dogs at each daily oral dose level of biskalcitrate potassium used in six month toxicity studies. The highest dose levels (converted to mg equivalents of Bi_2O_3) were 30 mg/kg and 18 mg/kg for rats and dogs, respectively. These dose levels corresponded to human equivalent doses (based upon relative body surface area) of 4.8 mg/kg and 10 mg/kg (rat and dog studies, respectively). The approximate mg equivalents of Bi_2O_3 per kg body weight for the human dosing regimen is 7 mg/kg (67 kg subject). Also cited were embryo-fetal development studies in rats and rabbits. No maternal and embryo-fetal effects were reported at any of the dose levels examined with the highest dose level to both rats and rabbits being 30 mg equivalents of Bi_2O_3 per kg body weight.

Biskalcitrate potassium can also be directly compared to bismuth subsalicylate (BSS; approved for over the counter use as the active ingredient in Pepto-Bismol) because potential human toxicity from either compound would result from excessive systemic levels of bismuth. The maximum recommended over the counter dose for BSS is approximately 4 g daily which corresponds to 2.3 g of bismuth. This level of bismuth is almost 5-fold greater than the mg equivalents of Bi_2O_3 contained in the proposed daily oral dose of biskalcitrate potassium in the Single Triple Capsules.

The sponsor submitted this NDA under Section 505 (b) (2) with reference to the approved Helidac® product (developed by Procter & Gamble under NDA 50-719 currently marketed by Prometheus Laboratories, Inc.) which contains BSS, metronidazole, and tetracyline as separate capsules. There are no revelant nonclinical safety issues with the clinical use of Helicide® for the eradication of *Helicobacter pylori*.

No additional Pharmacology/Toxicology NDA Review is provided beyond the Cover Sheet and Executive Summary.

Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Concurrence:

Kenneth Hastings, Dr. P.H., DABT
Pharmacology/Toxicology Supervisor & Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

cc:

HFD-590/CSO/L.Chan
HFD-590/MO/J.Meyer
HFD-590/Chem/G.Holbert
HFD-590/Micro/P.Dionne
HFD-590/Stat/R.Davi

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

/s/

Steve Hundley
9/27/02 08:45:37 AM
PHARMACOLOGIST

Kenneth Hastings
10/1/02 02:52:35 PM
PHARMACOLOGIST

Renata Albrecht
10/2/02 03:28:29 PM
MEDICAL OFFICER