CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-362

MEDICAL REVIEW(S)

Medical Officer Memo-to-File
Division of Metabolism and Endocrinology Products (HFD-510)

NDA: 22-362

Drug Name: Welchol (colesevelam) for Oral Suspension

Sponsor: Daiichi Sankyo, Inc.

Drug Class: Bile Acid Sequestrants

Proposed Indication: Primary Hyperlipidemia

Medical Reviewer: Eileen Craig, MD

Medical Team Leader: Eric Colman, MD

NDA 21-176 Welchol (colesevelam) Tablets Status=Approved May 26, 2000
NDA 21-141 Welchol (colsevelam) Capsules Status=Approved May 26, 2000
NDA 22-362 Welchol (colsevelam) for Oral Suspension Status=Pending

Subject: Correction of Status of PREA Pediatric Study Requirements for NDA 22-362, Welchol for Oral Suspension

This memo serves to clarify an incorrect statement in the June 11, 2009 clinical review of NDA 22-362. In this review, it was stated that a full waiver of the requirement to conduct pediatric studies was granted at the pre-NDA meeting.

NDA 22-362, submitted August 15, 2008, was found bioequivalent to the Tablet/Capsule formulations. The capsule formulation has never been marketed.

NDAs 21-176 and 21-141 each have the following outstanding postmarketing commitment (PMC):

1. Deferred pediatric study under PREA for the reduction of elevated LDL-cholesterol (LDL-C) in pediatric patients, (b) (4), with primary hypercholesterolemia (Frederickson Type IIa).

On October 5, 2001, the firm submitted the initial Written Request, which was sent in to both obtain pediatric exclusivity and to fulfill the above mentioned PMC. The most recent WR, dated April 2, 2007, specified a study in pediatric patients **ages 10 through 17 years** with heterozygous familial hypercholesterolemia (HeFH). This patient population is a subset of the hypercholesterolemia population with sufficient risk for CV disease to warrant treatment. There was, apparently, a verbal agreement between the agency and the sponsor to revise the age range of children to be studied.

Although the clinical review states that a waiver was granted for the powder formulation, this is not reflective of the pediatric studies that have been conducted with a bioequivalent formulation (the tablets). Therefore, pediatric studies for the powder formulation have been WAIVED for pediatric patients under age 10, and pediatric studies have been CONDUCTED for pediatric patients over aged 10 years and older.

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

/s/

Eileen Craig
6/23/2009 07:28:29 AM
MEDICAL OFFICER

Eric Colman
7/16/2009 09:01:53 AM
MEDICAL OFFICER

Medical Officer Review of NDA Submission

NDA#:	22-362
Applicant:	Daiichi Sankyo Pharma
Drug Product:	Welchol™ (colesevelam hydrochloride) for Oral Suspension
Dosage Form and Strength:	3.75 gram packet once daily or 1.875 gram packet twice daily
Stamp Date:	15-Aug-2008
PDUFA Date:	15-Jun-2009
Review Priority Classification:	Standard (S)
Indications:	Primary Hyperlipidemia and Type 2 Diabetes Mellitus
Review Date:	6/10/09

Background:

Welchol™ (colesevelam hydrochloride) for Oral Suspension is an alternate dosage form of colesevelam hydrochloride to the approved tablet and capsule formulations (NDA 21-176 and NDA 21-141, respectively). The active ingredient in the proposed alternate dosage form for colesevelam hydrochloride is the same the active ingredient in the currently marketed Welchol™ (colesevelam hydrochloride) Tablets, approved in NDA 21-176. In this submission the applicant provides an *in vitro* bioequivalence (BE) study between Welchol™ (colesevelam hydrochloride) for Oral Suspension and the commercial Welchol™ (colesevelam hydrochloride) Tablets. Welchol™ (colesevelam hydrochloride) for Oral Suspension has two product presentations resulting in two strengths: 1.875 g in a 2.65 g packet and 3.750 g in a 5.3 g packet, on an anhydrous basis. The 1.875 g/2.65 g packet and 3.750 g/5.3 g packet are equivalent to 3 Welchol™ (colesevelam hydrochloride) Tablets and 6 Welchol™ (colesevelam hydrochloride) Tablets, respectively.

Welchol (colesevelam hydrochloride) is a non-absorbed, lipid-lowering and glucose-lowering agent intended for oral administration. Welchol is a high-capacity bile acid-binding molecule and is approved for the following indications:

- as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia (Fredrickson Type

IIa) as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor.
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

No clinical studies of efficacy or safety were conducted for this application; therefore the drug-product will be limited to the indications approved for the reference product.

Summary of Clinical Biopharmaceutical Studies:

Please refer to the Clinical Pharmacology review by Jaya bharathi Vaidyanathan, Ph.D. for the detailed review.

This submission contains an *in vitro* bioequivalence (BE) study between colesevelam HCl powder for oral suspension and the commercial colesevelam HCl tablets. In a communication to the sponsor on Aug 30, 2004, the Agency agreed to this approach of establishing bioequivalence. The performance of the BE study followed the clinical development plan agreed to by FDA on August 31, 2004, and was in conformance with the 1998 FDA interim guidance, *Cholestyramine Powder In Vitro Bioequivalence.*

An *in vitro* bioequivalence study was conducted comparing Welchol™ (colesevelam hydrochloride) powder for oral suspension and Welchol™ (colesevelam hydrochloride) tablets. The two types of testing performed were equilibrium and kinetics both of which monitor the binding reaction between three bile acids, glycocholic acid (GC), glycochenodeoxycholic acid (GCDC) and taurodeoxycholic acid (TDC), with either Welchol™ powder for oral suspension or Welchol™ tablets. The samples were prepared from tablets or powder for oral suspension and testing was conducted as per the 1998 FDA interim guidance, *Cholestyramine Powder In Vitro Bioequivalence.*

According to the Clinical Pharmacology team, Welchol powder can be considered to be similar to Welchol tablets in terms of its binding characteristics. Based on the data provided in this submission, Welchol tablets and powder for oral suspension are equivalent.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 22-362 for Welchol for oral suspension (colesevelam HCl) and finds it acceptable.

Other Discipline Review Issues:
CMC:
Refer to Dr. Elsbeth Chikhale's review submitted to DFS for review details.

The recommendation from the standpoint of chemistry, manufacture and controls is APPROVAL based on:
- Acceptable drug substance quality
- Acceptable drug product quality

- Drug product stability data to support the proposed shelf life of 24 months
- Acceptable overall recommendation from the Office of Compliance

The CMC labeling comments are as follows:

- The PI should be consistent with above label, regarding the drug product name, Welchol (colesevelam HCl) for Oral Suspension (as suggested by DMEPA), therefore, in the PI the word (b) (4) should be removed from the name.
- Similarly, consistent with the carton and package label, the PI should indicate "add 1/2 cup to 1 cup (4 to 8 ounces) of water" in section 2.1 and section 2.2 and section 17 (dosing).
- For storage statement on cartons and package labels and PI section 16. I recommend to replace the word "to" by the word (b) (4), so the it will state: "......; excursions permitted (b) (4) 15-30....."

Evaluation of labeling: After incorporation of the above comments, the packets, cartons, and PI are acceptable from a CMC stand point.

Office of Pharmaceutical Science/Immediate Office
Refer to the review by Raanan A. Bloom, Ph.D. OPS/IO/PARS in DFS for details.

Review of Environmental Assessment
NDA 22-362 requests approval of Welchol™ (colesevelam hydrochloride) (b) (4) for Oral Suspension for treatment of primary hypercholesterolemia. An EA for related application NDA 21-141 for Welchol™ Tablets was previously reviewed and a FONSI was issued (2000). Upon approval of supplement S-017 to NDA 21-141 (2008), the FDA requested that an update to the Welchol™ EA be provided with future applications or supplements.The EA submitted with this application (NDA 22-362) is intended to address the request for updated information, and is to be considered as an add-on to the EA for NDA 21-141. The EA includes updated 5 year usage estimates, an updated aquatic assessment, and a new terrestrial assessment.

Based on an evaluation of the information provided in this EA and previous EAs, in FDA guidance, and on the scientific validity of the “no effects” conclusions of the EA, no significant adverse environmental impacts are expected from the introduction of colesevelam hydrochloride residues into the environment due approval of WelcholTM

A Finding of No Significant Impact (FONSI) is recommended.

Division of Medication Error Prevention and Analysis
Refer to the review by Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator in DFS for details.

Label and Labeling Review
This review outlines recommendations for packaging consideration, overlapping color schemes, presentation of the established name, presentation of the product strength and

net quantity, preparation instructions, presence of dosage form descriptor, and lack of product strength on side panel of carton labeling.

Two pertinent recommendations include the following:

- For the preparation instructions, revise the statement (b) (4) to read "Add 1/2 cup to 1 cup (4 to 8 ounces) of water." Patients may not be familiar with how to convert ounces into cups. Having this essential information presented in cups will also help to ensure patients add the correct amount of water while also providing adequate instructions to healthcare practitioners administering this product. (b) (4)
- Delete the dosage form descriptor (b) (4) above the proprietary name as this descriptor is unnecessary and inconsistent with the USP definition of this type of pharmaceutical dosage form which is 'for Oral Suspension'.

Other Administrative Issues:
Debarment:

Pursuant to the provisions of 21USC335a(k)(1), Daiichi Sankyo Inc. certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21USC335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above reference application.

Audits:
The Division of Scientific Investigations (DSI) inspection was initially consulted to inspect the study site for Study 2007-1315. However, as there is no commercial manufacturing site identified in this submission, the bioequivalence studies submitted in this application are not considered the pivotal BE studies. The DSI inspection request was withdrawn.

Financial Disclosure:
As there were no clinical studies conducted with Welchol™ for Oral Suspension, investigator financial disclosure information is not applicable.

The User Fee of $589,000 for the application has been paid under User Fee Number PD3008525. A check from Daiichi Sankyo to FDA for the amount of $589,000 dated 7/23/08 was submitted.

Pediatric Requirements:
Daiichi Sankyo provides reference to 21 CFR 314.55 for the purpose of requesting a waiver of submitting assessments of pediatric safety and effectiveness for Welchol (colesevelam HCl) (b) (4) for Oral Suspension. During the Type B Pre-NDA meeting on

March 13, 2008, the Agency agreed with the Sponsor's position that a waiver is justified for this dosage form as pediatric data will be submitted to NDA 21-176 (Welchol Tablets) for a bioequivalent dosage form.

(b) (4)

Tradename:

The applicant proposed to use the name Welchol™ (colesevelam hydrochloride) Powder for Oral Suspension

As noted above, the Division of Medication Error Prevention and Analysis recommends deleting the dosage form descriptor (b) (4) above the proprietary name as this descriptor is unnecessary and inconsistent with the USP definition of this type of pharmaceutical dosage form which is 'for Oral Suspension'.

Labeling:
The applicant has proposed the following changes (in red font) to the Welchol label and the clinical reviewer's additions are in yellow highlight and deletions in double strike-through.

(b) (4)

(C) 2 pages of labeling has been withheld immediately folloowing this page as B4 CCI/TS

Welchol™ (colesevelam hydrochloride) Tablets, 625 mg are a commercially available bile acid sequestrant that lowers cholesterol levels. Six tablets is the prescribed daily dose. The efficacy of colesevelam hydrochloride has been demonstrated in clinical studies. These studies are documented in the approved NDAs for capsule and tablet formulations of colesevelam hydrochloride (NDA 21-141 and NDA 21-176, respectively) and the labeling for these products. Welchol™ (colesevelam hydrochloride) for Oral Suspension is the proposed drug product that potentially provides once or twice daily dosing to achieve the same cholesterol lowering effect. In this application, Daiichi Sankyo Pharma Development has provided an *in vitro* bioequivalence (BE) study comparing the proposed Welchol™ (colesevelam hydrochloride) for Oral Suspension to the approved tablet formulation. The two types of testing performed were equilibrium and kinetics both of which monitor the binding reaction between three bile acids, glycocholic acid, glycochenodeoxycholic acid and taurodeoxycholic acid, with either Welchol™ (colesevelam hydrochloride) for Oral Suspension or Welchol™ (colesevelam hydrochloride) Tablets. The *in vitro* equivalency study was conducted using the proposed commercial formulation and manufacturing process for Welchol™ (colesevelam hydrochloride) for Oral Suspension. Based on the data, Welchol™ (colesevelam hydrochloride) for Oral Suspension and Welchol™ (colesevelam hydrochloride) Tablets have been shown to be equivalent.

Recommendations:
This 505(b)(1) application for Welchol™ (colesevelam hydrochloride) for Oral Suspension should be approved.

REVIEWED BY:
6/10/2009
Eileen Craig, MD
FDA/CDER/OND/ODEII/DMEP
Medical Officer

Eric Colman, MD
FDA/CDER/OND/ODEII/DMEP
Deputy Division Director and Medical Team Leader

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

/s/

Eileen Craig
6/10/2009 07:36:42 PM
MEDICAL OFFICER

Eric Colman
6/11/2009 10:21:12 AM
MEDICAL OFFICER
I concur with Dr. Craig's review