# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-362**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

*Office of Clinical Pharmacology*

*New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| NDA Number | 22-362 | Brand Name | Welchol |
| OCP Division (I, II, III, IV, V) | DCP II | Generic Name | colesevelam |
| Medical Division | DMEP | Drug Class | |
| OCP Reviewer | Lucun Bi, Ph.D. | Indication(s) | Type 2 Diabetic, hypercholesteramia |
| OCP Pharmacometrics Reviewer | - | Dosage Form | Powder for Oral Suspension |
| OCPB Team Leader | Sally Choe, Ph.D. | Dosing Regimen | |
| Date of Submission | 8/15, 2008 | Route of Administration | Oral administration |
| Estimated Due Date of OCP Review | May 8, 2009 | Sponsor | Daiichi Sankyo Pharma |
| PDUFA Due Date | June 15, 2009 | Priority Classification | Standard |
| Division Due Date | | | |

**Clin. Pharm. and Biopharm. Information**

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | | | | |
| **HPK Summary** | | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| ***Patients-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |

| | | | | |
|---|---|---|---|---|
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| In vitro BE study | X | 1 | **1** | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **1** | | |

**Filability**

| | **"X" if yes** | **Comments** |
|---|---|---|
| **Application filable?** | **X** | **Comments to the Sponsor: None** |
| **Submission in Brief:** See the details below. | **Reviewer's Comments:** **Clinical Pharmacology Review will focus on results of the in vitro bioequivalence (BE) study and the proposed labeling. No DSI inspection is requested for the in vitro BE study (KCM-2007- 1836-ANA) site and its analytical site.** | |

Submission in Brief:

Daiichi Sankyo, Inc. (The sponsor) submitted a new drug application (NDA 23-362) seeking FDA's approval of Welchol™ (colesevelam hydrochloride) in the form of powder for oral suspension (powder) to treat patients with hypercholesteramia and type 2 diabetic mellitus (T2DM).

Welchol™ was approved on May 26, 2000 as tablet (NDA 21-176) and capsule (NDA 21-141) formulations; the later has never been marketed. The recommended starting dose of Welchol™ is 3 tablets (625 mg each) taken twice per day with meals or 6 tablets once per day with a meal.

Welchol™ is a bile acid sequestrant indicated as an adjunct to diet and exercise to

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia as monotherapy or in combination with an hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (1.1).
- improve glycemic control in adults with type 2 diabetes mellitus.

The sponsor stated that Welchol™ (b) (4) formulation could potentially provide convenient once or twice daily dosing to achieve the same cholesterol lowering effect as compared to the tablet formulation. Welchol™ (b) (4) formulation has two presentations (strengths): 1.875 g in a 2.65 g packet and 3.750 g in a 5.3 g packet, which are equivalent to 3 and 6 Welchol™ tablets, respectively. Both presentations are manufactured from a (b) (4)

In the NDA submission, the sponsor presented the results of the in vitro binding assay of the bile salts to demonstrate the bioequivalence of the Welchol™ (b) (4) formulation to Welchol™ tablet formulation (Study KCM-2007-1836-ANA).

The in vitro BE approach by in vitro binding assay of bile salts was accepted by FDA in teleconference on March 13, 2008, and was in conformance with the 1998 FDA interim guidance titled: "Cholestyramine Powder In Vitro Bioequivalence". The sponsor conducted both equilibrium study and kinetics study, in which the sponsor monitored the binding reaction of three bile acids, glycocholic acid, glycochenodeoxycholic acid and taurodeoxycholic acid, with either Welchol™ (b) (4) formulation or Welchol™ tablets. The in vitro BE study includes the following components:

- The equilibrium studies were conducted at the constant time and varying the concentration of bile acids with or without acid treatment. (b) (4)
- The kinetic studies were conducted with varying reaction time while holding the constant bile salt concentration at 0.3 M and 3 M. (b) (4)
- Both studies were performed in a dissolution apparatus (b) (4)
- All the results were submitted in study report (Study KCM-2007-1836-ANA).

The following are the list of analytical methods and the associate validation reports:

(b) (4)

The in vitro BE study was conducted using Welchol™ powder manufactured with the proposed commercial formulation and manufacturing process. The sponsor also submitted analytical procedures and validation reports in the final study report.

The sponsor indicated that the storage and retest period of colesevelam hydrochloride drug substance was supported by the approved NDA 21-141 and NDA 21-176.

In the teleconference on March 13, 2008, the sponsor requested a waiver for the need for evaluation of Welchol™ powder formulation in the pediatric population, and stated that the pediatric data for the tablet dosage form would be submitted to NDA 21-176 (Welchol™ Tablets). FDA agreed with the Sponsor's position that a waiver was justified for the Welchol™ powder formulation.

The sponsor also submitted the annotated draft labeling, in word document, in PDF and in SPL format. The approved labeling text for Welchol was also attached.

(G) 3 pages of Biopharm has been withheld in full immediately following this pages as B4 CCI/TS

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

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Lucun Bi
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Sally Choe
12/12/2008 01:14:06 PM
BIOPHARMACEUTICS

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 22-362 | Submission Date(s): 8/15/08 |
| Brand Name | Welchol™ |
| Generic Name | Colesevelam hydrochloride |
| Reviewer | Jaya bharathi Vaidyanathan, Ph.D. |
| Team Leader (Acting) | Wei Qiu, Ph.D. |
| OCP Division | DCP-2 |
| OND Division | Metabolic and Endocrine Products |
| Sponsor | Daiichi Sankyo Pharma |
| Submission Type; Code | 505 (b) (2) Standard |
| Formulation; Strength(s) | Powder for oral suspension |
| Indication | • Reduce elevated LDL-C in patients with primary hypercholesterolemia as monotherapy or in combination with an HMG CoA reductase inhibitor.<br>• Improve glycemic control in adults with type 2 diabetes mellitus |

## Table of Contents

# 1 Executive Summary

Daiichi Sankyo has submitted an original New Drug Application (NDA) for Welchol™ (colesevelam hydrochloride) (b) (4) for Oral Suspension. The sponsor is seeking approval of the powder for oral suspension as an alternate dosage form to the marketed Welchol™ tablets, NDA 21-176 and is proposing a single Welchol™ package insert based on the currently approved tablet labeling with appropriate sections modified to incorporate the powder for oral suspension dosage form.

Welchol™ (colesevelam hydrochloride) is a bile acid sequestrant and is indicated as an adjunct to diet and exercise to:

- Reduce elevated low density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia as monotherapy or in combination with an hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitor.
- Improve glycemic control in adults with type 2 diabetes mellitus.

The sponsor is currently marketing Welchol in tablets formulation containing 625 mg of colesevelam HCl. Colesevelam HCl is non-absorbed polymer that acts locally in the gastrointestinal tract to bind the salts of bile acids. This action causes a compensatory increase in cholesterol biosynthesis in liver and enhanced oxidation of cholesterol to bile acids and an upregulation of LDL receptors, leading to decreased serum LDL-cholesterol. According to sponsor, although Welchol tablets are well-tolerated, some patients find them difficult to swallow due to the large size of the tablets and the number of tablets required. Approved doses are 6 to 7 tablets per day, corresponding to doses of 3.75 g or 4.375 g of colesevelam HCl, respectively. The sponsor has developed this powder formulation providing 4.375 g of colesevelam HCl in a packet with excipients that aid palatability and powder flow.

In the original submissions of Welchol NDA, the sponsor demonstrated comparable binding properites of the capsule and tablet formulations using in vitro assays of bile acid salt binding kinetics and binding isotherms. The tablet formulation (NDA 21-176) was approved along with the capsule formulation (NDA 21-141). The capsule formulation was never marketed. The sponsor has used a similar approach to gain approval for this new sachet formulation. 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.*

## 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 22-362 for Welchol (b) (4) for oral suspension (colesevelam HCl) and finds it acceptable. OCP intra-division briefing was held on June 8, 2009. The attendees were Drs.

Chandra Sahajwalla, Suresh Doddapaneni, Wei Qiu, Jaya bharathi Vaidyanathan, Issam Zineh, Mike Pacanowski, Ritesh Jain, Immo Zdrojewski, Zhihong Li, and Ting Ong.

### 1.2 Phase IV Commitments

None.

### 1.3 Summary of CPB findings

Six to seven tablets (625 mg each) is the prescribed daily dose for Welchol™ (colesevelam hydrochloride). Welchol powder for oral suspension is the proposed drug product that is proposed to potentially provide convenient once or twice daily dosing to achieve the same cholesterol lowering effect. 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.*

Table 1 below summarizes the mean millimoles of each bile acid per gram of colesevelam hydrochloride (x/m) and the ratio of the average percent of each bile acid bound for Welchol (b) (4) (T) and Welchol Tablets (R) at different concentrations. The T/R ratios for GC, GCDC and TRC of 0.97, 0.96 and 0.98, respectively, show very close agreement between the Powder and Tablets.

**Table 1: Summary of Equilibrium Study without acid pretreatment. Mean millimoles of each bile acid per gram of resin (x/m), mean percent and ratio of each bile acid bound for Welchol (b) (4) (T) and Welchol Tablets (R)**

| | | | GC | | |
|---|---|---|---|---|---|
| **Total Initial Conc. mM** | **x/m Powder** | **x/m Tablets** | **Average % Bound Powder (T)** | **Average % Bound Tablets (R)** | **T/R** |
| 0.1 | 0.039 | 0.039 | 90.7 | 90.7 | 1.00 |
| 0.3 | 0.108 | 0.110 | 83.7 | 85.3 | 0.98 |
| 1 | 0.243 | 0.255 | 56.6 | 59.4 | 0.95 |
| 3 | 0.593 | 0.604 | 46.1 | 47.0 | 0.98 |
| 7 | 1.241 | 1.157 | 41.4 | 38.6 | 1.07 |
| 10 | 0.922 | 1.095 | 21.5 | 25.5 | 0.84 |
| 20 | 1.000 | 1.101 | 11.7 | 12.8 | 0.91 |
| 30 | 1.378 | 1.387 | 10.7 | 10.8 | 0.99 |
| | | | | Mean T/R | 0.97 |

| Total Initial Conc. mM | | | GCDC | | |
|---|---|---|---|---|---|
| | x/m Powder | x/m Tablet | Average % Bound Powder (T) | Average % Bound Tablets (R) | T/R |
| 0.1 | 0.043 | 0.043 | 100.0 | 100.0 | 1.00 |
| 0.3 | 0.126 | 0.124 | 97.7 | 96.9 | 1.01 |
| 1 | 0.386 | 0.391 | 90.0 | 91.4 | 0.99 |
| 3 | 1.135 | 1.147 | 88.2 | 89.3 | 0.99 |
| 7 | 2.579 | 2.607 | 85.9 | 87.0 | 0.99 |
| 10 | 3.015 | 3.281 | 70.3 | 76.6 | 0.92 |
| 20 | 2.82 | 3.177 | 32.9 | 37.1 | 0.89 |
| 30 | 2.679 | 3.027 | 20.8 | 23.6 | 0.88 |
| | | | | Mean T/R | 0.96 |

| Total Initial Conc. mM | | | TDC | | |
|---|---|---|---|---|---|
| | x/m Powder | x/m Tablet | Average % Bound Powder (T) | Average % Bound Tablets(R) | T/R |
| 0.1 | 0.014 | 0.014 | 100.0 | 100.0 | 1.00 |
| 0.3 | 0.043 | 0.043 | 100.0 | 100.0 | 1.00 |
| 1 | 0.134 | 0.135 | 93.7 | 94.4 | 0.99 |
| 3 | 0.4 | 0.401 | 93.2 | 93.5 | 1.00 |
| 7 | 0.923 | 0.927 | 92.2 | 92.6 | 1.00 |
| 10 | 1.16 | 1.216 | 81.1 | 85.0 | 0.95 |
| 20 | 1.276 | 1.382 | 44.6 | 48.3 | 0.92 |
| 30 | 1.302 | 1.385 | 30.4 | 32.3 | 0.94 |
| | | | | Mean T/R | 0.98 |

The T/R ratios of means for total bile salt (GC+GCDC+TDC) binding ranged from 0.9 – 1.1 at 0.1 – 30 mM concentrations (Table 2).

**Table 2: Statistical analysis for total bile salts binding (GC+GCDC+TDC) (mmoles/g) at Equilibrium without acid pretreatment for Welchol powder (Test) and Welchol tablet (reference)**

| Initial Bile Salts Conc (mM) | Powder (Test) (GC+GCDC+TDC) (Mean) | Tablet (Reference) (GC+GCDC+TDC) (Mean) | Ratio (Test/Reference) |
|---|---|---|---|
| 0.1 | 0.096 | 0.096 | 1 |
| 0.3 | 0.277 | 0.277 | 1 |

| | | | |
|---|---|---|---|
| 1 | 0.763 | 0.781 | 0.976 |
| 3 | 2.128 | 2.152 | 0.988 |
| 7 | 4.743 | 4.691 | 1.011 |
| 10 | 5.097 | 5.592 | 0.911 |
| 20 | 5.096 | 5.66 | 0.900 |
| 30 | 5.359 | 5.799 | 0.924 |

The results of the comparison using Langmuir isotherms **without** acid pre-treatment are shown in the table below. This was used as the pivotal bioequivalence measure in the original NDA submission to bridge the capsule formulation to the tablet formulations of Welchol. The results indicate that the affinity (*k1*) and binding capacity (*k2*) are comparable (± 20%) for the two formulations. [*Note: The sum of the mean constants of the three bile acids (GC+GCDC+TDC) from powder was compared to the sum of the constants from the tablet formulation.*] The individual 90% CI for the capacity constant is also shown below. As indicated the 90% CI for GCDC and TDC was within the 80-120% interval used in the approval of ANDA, however for the GC, this was slightly below (77.6 – 117.3).

**Table 3: Langmuir isotherm parameters**

| **Parameter** | **Type** | **Dosage Form** | | **Powder/ Tablets** | **90% CI for Ratio** |
|---|---|---|---|---|---|
| | | Powder Estimate ± SE | Tablets Estimate ± SE | | |
| Affinity Constant (k1) | GC | 1.53 ± 1.113 | 1.75 ± 0.970 | 0.87 | NA |
| | GCDC | 13.56 ± 16.016 | 9.67 ± 7.238 | 1.40 | NA |
| | TDC | 17.81 ± 3.225 | 18.72 ± 3.815 | 0.95 | NA |
| Capacity Constant (k2) | GC | 1.31 ± 0.114 | 1.36 ± 0.080 | 0.96 | 77.6 – 117.3 |
| | GCDC | 2.74 ± 0.053 | 3.10 ± 0.056 | 0.88 | 83.7 – 93.1 |
| | TDC | 1.33 ± 0.010 | 1.42 ± 0.011 | 0.94 | 91.6 – 95.8 |

The results of comparison using Langmuir isotherm **with** acid pre-treatment are shown below. The results indicate that the affinity (*k1*) and binding capacity (*k2*) are comparable (± 20%) for the two formulations. [*Note: The sum of the mean constants of the three bile acids (GC+GCDC+TDC) from powder was compared to the sum of the constants from the tablet formulation.*]

| Dosage form | $k_1$ | | |
|---|---|---|---|
| | GC | GCDC | TDC |
| Oral Powder | 4.03 | 11.01 | 22.29 |
| Tablets | 2.55 | 14.94 | 26.29 |

| Dosage form | $k_2$ | | |
|---|---|---|---|
| | GC | GCDC | TDC |
| Oral Powder | 0.89 | 2.85 | 1.28 |
| Tablets | 1.18 | 2.95 | 1.31 |

In addition, the amount of bile acids bound and the percent bound for the two formulations was comparable.

The comparison of kinetic data of binding of 0.3 mM bile acid salts [0.13 mM GC (39.29 mg; 0.13 mM GCDC (37.98 mg); 0.04 mM TDC (14.01 mg)] with Welchol powder and tablets and the comparison of kinetic data of binding of 3.0 mM bile acid salts [1.27 mM GC (392.92 mg; 1.27 mM GCDC (379.76 mg); 0.43 mM TDC (140.06 mg)] with Welchol powder and tablets was conducted. The binding at the initial 0.3 mM concentration was extremely rapid for both dosage forms. The results for both concentrations were extremely reproducible. Additionally, the kinetic binding of 0.3 mM and 3.0 mM bile salts for both dosage forms was nearly identical.

Overall the T/R ratio for the total bile salt binding is acceptable. Also, the 90% CI for the capacity constant (k2) for the bile salts are within 80-120% except for one component GC (77.6 – 117.3) and therefore, Welchol powder can be considered to be similar to Welchol tablets in terms of its binding characteristics

# 2 QBR

## 2.1 General Attributes

Welchol™ (b) (4) 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 fill weights compensate for a moisture content of 6% (based on observed moisture values in the (b) (4). The 1.875 g/2.65 g packet and 3.750 g/5.3 g packet are equivalent to three Welchol tablets and six Welchol tablets, respectively. Both presentations are manufactured from a common blend.

**Table 4: Composition of Welchol powder for oral suspension**

| Ingredient | Formula % | Quantity (g/packet) | | Function | Reference |
|---|---|---|---|---|---|
| | | 2.65 g Packet[a] | 5.3 g Packet[a] | | |
| Colesevelam Hydrochloride | 75.00%[b] | 1.875[c] | 3.750[c] | Active | In-House |
| Lemon Flavor | (b) (4) | (b) (4) | (b) (4) | (b) (4) | In-House (b) (4) |
| Citric Acid | | | | | USP |
| Magnesium Trisilicate | | | | | USP |
| Aspartame | | | | | NF |
| Simethicone (b) (4) | | | | | In-House (b) (4) |
| Orange Flavor | | | | | In-House (b) (4) |
| Medium-Chain Triglycerides (b) (4) | | | | | NF |
| Propylene Glycol Alginate (b) (4) | | | | | NF |
| Total | 100.00% | 2.50[a] | 5.00[a] | | |

The product is currently packaged into single dose, child-resistant and non-child-resistant packets.

## 2.2 General Clinical Pharmacology

As indicated in the pre-NDA teleconference meeting minutes, no clinical and clinical pharmacology studies were required for Welchol™ (b) (4) for oral suspension.

## 2.3 General Biopharmaceutics

This submission contains an *in vitro* study to address the bioequivalence (BE) between colesevelam HCl powder for oral suspension and the commercial colesevelam HCl 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 protocol described in the 'Interim Guidance Cholestyramine Powder *in vitro* Bioequivalence' (1998 Guidance), was used with some minor modifications to account for the differences in the two dosage forms. The modifications included scaling up the volumes used for testing while maintaining the same concentrations, and the use of dissolution vessels to facilitate the reactions and to maintain temperature. The equilibrium testing was performed by (b) (4) and the kinetics testing was performed by (b) (4) Both labs used the same sample lots of Welchol powder for oral suspension and Welchol tablets for testing.

**1. Equilibrium binding:** The equilibrium sample testing was performed using test method (b) (4). This method determines the equilibrium of binding of three bile salts, GC, GCDC and TDC, with either Welchol powder for oral suspension or Welchol tablets. (b) (4)

*Equilibrium without Acid Pretreatment*

The entire equilibrium test procedure without acid pretreatment was repeated six times each for the Welchol powder for oral suspension and Welchol tablet dosage forms. For the Welchol powder for oral suspension, one packet was used for each sample set of eight concentrations and an equivalent of 80 mg of active ingredient (~107 mg) was used for testing in each vessel. For the Welchol tablets, a tablet composite sample was prepared by grinding 20 tablets and weighing out an amount equivalent to 80 mg of active ingredient (~118 mg) based on the average tablet weight. This 118 mg of tablet powder was used for testing in each vessel. The initial concentrations of bile acids GC, GCDC and TDC were the same for both the Welchol powder for oral suspension and Welchol tablet dosage forms. The amount of bile acid salt bound to the active ingredient (Colesevelam) was calculated from the difference between the initial

concentrations of the bile acid salts added to the Welchol and the concentrations present in the filtrate at the end of the binding experiment.

Based on the guidance, the parameters to be reported for both the test and reference products include, percent binding of bile acid salt, micromoles of bile acid salts bound, affinity constant *k1*, capacity constant *k2* and the coefficient of determination r2 (when linear regression is used to determine *k1* and *k2*). Tables 5 and 6 contain the average results and data treatment for six replicate determinations for Welchol powder and tablets respectively.

**Table 5: Summary of equilibrium binding of bile acid salts to Welchol from powder formulation in pH 6.8 phosphate buffer without acid pretreatment (Mean of six determinations).**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g |
| 0.1 | 0.043 | 0.004 | 0.039 | 0.043 | 0.000 | 0.043 | 0.014 | 0.000 | 0.014 |
| 0.3 | 0.129 | 0.021 | 0.108 | 0.129 | 0.003 | 0.126 | 0.043 | 0.000 | 0.043 |
| 1 | 0.429 | 0.186 | 0.243 | 0.429 | 0.043 | 0.386 | 0.143 | 0.009 | 0.134 |
| 3 | 1.286 | 0.693 | 0.593 | 1.287 | 0.152 | 1.135 | 0.429 | 0.029 | 0.400 |
| 7 | 3.000 | 1.759 | 1.241 | 3.004 | 0.425 | 2.579 | 1.001 | 0.078 | 0.923 |
| 10 | 4.286 | 3.364 | 0.922 | 4.291 | 1.276 | 3.015 | 1.430 | 0.270 | 1.160 |
| 20 | 8.573 | 7.573 | 1.000 | 8.582 | 5.762 | 2.820 | 2.860 | 1.584 | 1.276 |
| 30 | 12.859 | 11.481 | 1.378 | 12.874 | 10.195 | 2.679 | 4.289 | 2.987 | 1.302 |

**Table 6: Summary of equilibrium binding of bile acid salts to Welchol from tablet formulation in pH 6.8 phosphate buffer without acid pretreatment (Mean of six determinations).**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g |
| 0.1 | 0.043 | 0.004 | 0.039 | 0.043 | 0.000 | 0.043 | 0.014 | 0.000 | 0.014 |
| 0.3 | 0.129 | 0.019 | 0.110 | 0.128 | 0.004 | 0.124 | 0.043 | 0.000 | 0.043 |
| 1 | 0.429 | 0.174 | 0.255 | 0.428 | 0.037 | 0.391 | 0.143 | 0.008 | 0.135 |
| 3 | 1.286 | 0.682 | 0.604 | 1.284 | 0.137 | 1.147 | 0.429 | 0.028 | 0.401 |
| 7 | 3.001 | 1.844 | 1.157 | 2.997 | 0.390 | 2.607 | 1.001 | 0.074 | 0.927 |
| 10 | 4.288 | 3.193 | 1.095 | 4.282 | 1.001 | 3.281 | 1.430 | 0.214 | 1.216 |
| 20 | 8.575 | 7.474 | 1.101 | 8.563 | 5.386 | 3.177 | 2.859 | 1.477 | 1.382 |
| 30 | 12.863 | 11.476 | 1.387 | 12.845 | 9.818 | 3.027 | 4.289 | 2.904 | 1.385 |

Tables 7 and 8 contain the average results and data treatment for six replicate determinations for the percent bound for Welchol powder and tablets respectively.

**Table 7: Percent binding results for Welchol powder for oral suspension in the equilibrium binding study without acid pretreatment**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol |
| 0.1 | 90.7 | 0.039 | 1.9 | 100.0 | 0.043 | 2.0 | 100.0 | 0.014 | 0.7 |
| 0.3 | 83.7 | 0.108 | 5.3 | 97.7 | 0.126 | 5.9 | 100.0 | 0.043 | 2.2 |
| 1 | 56.6 | 0.243 | 11.8 | 90.0 | 0.386 | 18.2 | 93.7 | 0.134 | 7.0 |
| 3 | 46.1 | 0.593 | 28.9 | 88.2 | 1.135 | 53.5 | 93.2 | 0.400 | 20.9 |
| 7 | 41.4 | 1.241 | 60.5 | 85.9 | 2.579 | 121.6 | 92.2 | 0.923 | 48.2 |
| 10 | 21.5 | 0.922 | 45.0 | 70.3 | 3.015 | 142.2 | 81.1 | 1.160 | 60.5 |
| 20 | 11.7 | 1.000 | 48.8 | 32.9 | 2.820 | 133.0 | 44.6 | 1.276 | 66.6 |
| 30 | 10.7 | 1.378 | 67.2 | 20.8 | 2.679 | 126.3 | 30.4 | 1.302 | 67.9 |

**Table 8: Percent binding results for Welchol tablets in the equilibrium binding study without acid pretreatment**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol |
| 0.1 | 90.7 | 0.039 | 1.9 | 100.0 | 0.043 | 2.0 | 100.0 | 0.014 | 0.7 |
| 0.3 | 85.3 | 0.110 | 5.4 | 96.9 | 0.124 | 5.8 | 100.0 | 0.043 | 2.2 |
| 1 | 59.4 | 0.255 | 12.4 | 91.4 | 0.391 | 18.4 | 94.4 | 0.135 | 7.0 |
| 3 | 47.0 | 0.604 | 29.5 | 89.3 | 1.147 | 54.1 | 93.5 | 0.401 | 20.9 |
| 7 | 38.6 | 1.157 | 56.4 | 87.0 | 2.607 | 122.9 | 92.6 | 0.927 | 48.4 |
| 10 | 25.5 | 1.095 | 53.4 | 76.6 | 3.281 | 154.7 | 85.0 | 1.216 | 63.4 |
| 20 | 12.8 | 1.101 | 53.7 | 37.1 | 3.177 | 149.8 | 48.3 | 1.382 | 72.1 |
| 30 | 10.8 | 1.387 | 67.6 | 23.6 | 3.027 | 142.8 | 32.3 | 1.385 | 72.3 |

The amount of bile acid bound was then used to evaluate the binding parameters by using the Langmuir equation:

$$\frac{x}{m} = \frac{k_1 k_2 Ceq}{1 + k_1 Ceq}$$

Where Ceq is the concentration of the bile acid salt remaining in solution (unbound), x is the amount of bile acid salt bound to the Welchol and m is the amount of Welchol used. The x/m ratio is the binding capacity of Welchol. The constant $k_1$ is defined as the adsorption coefficient or affinity constant and is related to the relative strength of the binding. The constant $k_2$ is the capacity constant and indicates the apparent maximum binding capacity of the tested material. The comparison of these constants is summarized in Table 9.

**Table 9: Comparison of the Langmuir isotherm parameters**

| **Parameter** | **Type** | **Dosage Form** | | **Powder/ Tablets** | **90% CI for Ratio** |
|---|---|---|---|---|---|
| | | Powder Estimate ± SE | Tablets Estimate ± SE | | |
| Affinity Constant (k1) | GC | 1.53 ± 1.113 | 1.75 ± 0.970 | 0.87 | NA |
| | GCDC | 13.56 ± 16.016 | 9.67 ± 7.238 | 1.40 | NA |
| | TDC | 17.81 ± 3.225 | 18.72 ± 3.815 | 0.95 | NA |
| Capacity Constant (k2) | GC | 1.31 ± 0.114 | 1.36 ± 0.080 | 0.96 | 77.6 – 117.3 |
| | GCDC | 2.74 ± 0.053 | 3.10 ± 0.056 | 0.88 | 83.7 – 93.1 |
| | TDC | 1.33 ± 0.010 | 1.42 ± 0.011 | 0.94 | 91.6 – 95.8 |

As indicated in the above table, the 90% CI for GCDC and TDC was within the 80-120% interval used in the approval of ANDA, however for the GC, this was slightly below (77.6 – 117.3). The overall *k1* (GC+GCDC+TDC) and *k2* (GC+GCDC+TDC) for powder and tablet was comparable (± 20%). Additionally, the different parameters (micromoles of bile acid salts bound, percent binding of bile acids and the constants *k1*, and *k2*) indicate that the binding capacities of both dosage forms at several initial concentrations (ranging from 0.1 to 30 mM) are very similar and there was no significant difference in the binding performances of both dosage forms in this study. The binding of GC with powder and tablet demonstrated an $r^2$ of 0.96 and 0.98, respectively, while for GCDC and TDC it was > 0.99 for both formulations.

*Equilibrium with Acid Pretreatment*

The equilibrium testing was performed per method QM3369 using the same procedure as stated above with the addition of an acid pretreatment. The acid pretreatment was performed by soaking the Welchol tablet powder grind or the Welchol powder for oral suspension in 0.1 N HCl for an hour at room temperature. The pH of the sample solutions was then adjusted to 6.8 with 1 N NaOH and pH 6.8 phosphate buffer (SIF) was added to bring the total solution volume up to 16 mL. The sample solutions were then allowed to soak overnight at room temperature. After the overnight soaking the samples were treated in a similar manner to the procedure detailed in the Equilibrium without acid treatment.

Based on the guidance the parameters to be reported for this experiment include the percent binding of bile acid salt at each time point and the micromoles of bile acid salt bound. Tables 10 and 11 contain the average results and data treatment for six replicate determinations for Welchol powder and tablets respectively.

**Table 10: Summary of equilibrium binding of bile acid salts to Welchol from powder formulation in pH 6.8 phosphate buffer with acid pretreatment (Mean of six determinations).**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g |
| 0.1 | 0.043 | 0.005 | 0.038 | 0.043 | 0.000 | 0.043 | 0.014 | 0.000 | 0.014 |
| 0.3 | 0.129 | 0.022 | 0.107 | 0.129 | 0.003 | 0.126 | 0.043 | 0.000 | 0.043 |
| 1 | 0.429 | 0.178 | 0.251 | 0.430 | 0.039 | 0.391 | 0.143 | 0.007 | 0.136 |
| 3 | 1.286 | 0.703 | 0.583 | 1.289 | 0.145 | 1.144 | 0.430 | 0.029 | 0.401 |
| 7 | 3.001 | 1.986 | 1.015 | 3.008 | 0.463 | 2.545 | 1.003 | 0.093 | 0.910 |
| 10 | 4.288 | 3.421 | 0.867 | 4.298 | 1.228 | 3.070 | 1.434 | 0.267 | 1.167 |
| 20 | 8.575 | 7.828 | 0.747 | 8.595 | 5.715 | 2.880 | 2.867 | 1.604 | 1.263 |
| 30 | 12.863 | 11.938 | 0.925 | 12.893 | 10.094 | 2.799 | 4.301 | 3.042 | 1.259 |

**Table 11: Summary of equilibrium binding of bile acid salts to Welchol from tablet formulation in pH 6.8 phosphate buffer with acid pretreatment (Mean of six determinations).**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g | Initial mM | Unbound mM | Bound mmol/g |
| 0.1 | 0.043 | 0.003 | 0.040 | 0.043 | 0.000 | 0.043 | 0.014 | 0.000 | 0.014 |
| 0.3 | 0.129 | 0.018 | 0.111 | 0.129 | 0.003 | 0.126 | 0.043 | 0.000 | 0.043 |
| 1 | 0.429 | 0.169 | 0.260 | 0.428 | 0.036 | 0.392 | 0.143 | 0.008 | 0.135 |
| 3 | 1.286 | 0.679 | 0.607 | 1.285 | 0.136 | 1.149 | 0.429 | 0.028 | 0.401 |
| 7 | 3.000 | 1.833 | 1.167 | 2.999 | 0.384 | 2.615 | 1.001 | 0.076 | 0.925 |
| 10 | 4.285 | 3.197 | 1.088 | 4.284 | 0.990 | 3.294 | 1.429 | 0.213 | 1.216 |
| 20 | 8.570 | 7.626 | 0.944 | 8.569 | 5.479 | 3.090 | 2.859 | 1.526 | 1.333 |
| 30 | 12.855 | 11.626 | 1.229 | 12.853 | 9.976 | 2.877 | 4.288 | 3.007 | 1.281 |

Tables 12 and 13 contain the average results and data treatment for six replicate determinations for the percent of Welchol powder and tablets respectively bound to bile acid salts.

**Table 12: Percent binding results for Welchol powder for oral suspension with acid pretreatment**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol |
| 0.1 | 88.4 | 0.038 | 1.9 | 100.0 | 0.043 | 2.0 | 100.0 | 0.014 | 0.7 |
| 0.3 | 82.9 | 0.107 | 5.2 | 97.7 | 0.126 | 5.9 | 100.0 | 0.043 | 2.2 |
| 1 | 58.5 | 0.251 | 12.2 | 90.9 | 0.391 | 18.4 | 95.1 | 0.136 | 7.1 |
| 3 | 45.3 | 0.583 | 28.4 | 88.8 | 1.144 | 54.0 | 93.3 | 0.401 | 20.9 |
| 7 | 33.8 | 1.015 | 49.5 | 84.6 | 2.545 | 120.0 | 90.7 | 0.910 | 47.5 |
| 10 | 20.2 | 0.867 | 42.3 | 71.4 | 3.070 | 144.8 | 81.4 | 1.167 | 60.9 |
| 20 | 8.7 | 0.747 | 36.4 | 33.5 | 2.880 | 135.8 | 44.1 | 1.263 | 65.9 |
| 30 | 7.2 | 0.925 | 45.1 | 21.7 | 2.799 | 132.0 | 29.3 | 1.259 | 65.7 |

**Table 13: Percent binding results for Welchol tablets with acid pretreatment**

| Total Initial Conc. mM | GC | | | GCDC | | | TDC | | |
|---|---|---|---|---|---|---|---|---|---|
| | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol | % Bile Acid Salt Bound vs. Initial Amount | Bile Acid Salt Bound Amount (mmol/g) | % Bile Acid Salt Bound vs. mg of Welchol |
| 0.1 | 93.0 | 0.040 | 2.0 | 100.0 | 0.043 | 2.0 | 100.0 | 0.014 | 0.7 |
| 0.3 | 86.0 | 0.111 | 5.4 | 97.0 | 0.126 | 5.9 | 100.0 | 0.043 | 2.2 |
| 1 | 60.6 | 0.260 | 12.7 | 91.6 | 0.392 | 18.5 | 94.4 | 0.135 | 7.0 |
| 3 | 47.2 | 0.607 | 29.6 | 89.4 | 1.149 | 54.2 | 93.5 | 0.401 | 20.9 |
| 7 | 38.9 | 1.167 | 56.9 | 87.2 | 2.615 | 123.3 | 92.4 | 0.925 | 48.3 |
| 10 | 25.4 | 1.088 | 53.1 | 76.9 | 3.294 | 155.3 | 85.1 | 1.216 | 63.4 |
| 20 | 11.0 | 0.944 | 46.0 | 36.1 | 3.090 | 145.7 | 46.6 | 1.333 | 69.5 |
| 30 | 9.6 | 1.229 | 59.9 | 22.4 | 2.877 | 135.7 | 29.9 | 1.281 | 66.8 |

Overall, the bile acid binding isotherms were very similar with acid pretreatment. The binding capacities of both dosage forms at several initial concentrations (0.1 to 30 mM) were determined. The results were comparable between the two formulations.

**Table 14: Comparison of the Langmuir isotherm parameters (**The constant $k_1$ is defined as the adsorption coefficient or affinity constant and is related to the relative strength of the binding. The constant $k_2$ is the capacity constant and indicates the apparent maximum binding capacity of the tested material).

| Dosage form | $k_1$ | | |
|---|---|---|---|
| | GC | GCDC | TDC |
| Oral Powder | 4.03 | 11.01 | 22.29 |
| Tablets | 2.55 | 14.94 | 26.29 |
| | | | |
| Dosage form | $k_2$ | | |
| | GC | GCDC | TDC |
| Oral Powder | 0.89 | 2.85 | 1.28 |
| Tablets | 1.18 | 2.95 | 1.31 |

The overall *k1* (GC+GCDC+TDC) and *k2* (GC+GCDC+TDC) for powder and tablet was comparable (± 20%).

*Comments:* Based on these data Welchol powder for oral suspension is comparable to Welchol tablets in the equilibrium study of bile acid salt binding in simulated intestinal fluid (pH 6.8 phosphate buffer) without acid pretreatment (pivotal measure).

***2.*** **Kinetic binding:** The kinetics sample testing was performed using method (b) (4)

(b) (4)

The sampling time intervals were the same as found in the Guidance. Each dosage form achieved equilibrium by 30 minutes. The amount of bile acid salt bound to Welchol was calculated from the difference between the initial concentrations of the bile acid salts added and the concentrations present in the filtrate at the end of the binding experiment.

The comparison of kinetic data of binding of 0.3 mM bile acid salts [0.13 mM GC (39.29 mg; 0.13 mM GCDC (37.98 mg); 0.04 mM TDC (14.01 mg)] with Welchol powder and tablets is shown below.

**Table 15: Comparison of kinetic data of binding of 0.3 mM bile acid salts**

| Time (min.) | Bound, mg | | | | | |
|---|---|---|---|---|---|---|
| | GC | | GCDC | | TDC | |
| | Oral Powder | Tablets | Oral Powder | Tablets | Oral Powder | Tablets |
| 3 | 31.3 | 30.6 | 34.7 | 33.7 | 13.6 | 12.6 |
| 6 | 33.5 | 33.4 | 35.5 | 35.1 | 13.7 | 13.1 |
| 9 | 34.3 | 34.4 | 35.9 | 35.6 | 13.7 | 13.3 |
| 12 | 34.7 | 34.8 | 36.1 | 35.9 | 13.7 | 13.4 |
| 15 | 35.0 | 35.1 | 36.2 | 36.0 | 13.7 | 13.4 |
| 30 | 35.5 | 35.7 | 36.4 | 36.3 | 13.7 | 13.5 |
| 60 | 35.9 | 36.1 | 36.5 | 36.5 | 13.7 | 13.6 |
| 120 | 36.1 | 36.3 | 36.6 | 36.6 | 13.7 | 13.6 |
| 240 | 36.3 | 36.5 | 36.7 | 36.7 | 13.7 | 13.6 |
| 480 | 36.2 | 36.5 | 36.7 | 36.7 | 13.7 | 13.7 |
| 960 | 36.2 | 36.5 | 36.8 | 36.8 | 13.7 | 13.7 |
| 1440 | 36.2 | 36.5 | 36.8 | 36.8 | 13.7 | 13.7 |

The comparison of kinetic data of binding of 3.0 mM bile acid salts [1.27 mM GC (392.92 mg; 1.27 mM GCDC (379.76 mg); 0.43 mM TDC (140.06 mg)] with Welchol powder and tablets is shown below.

**Table 16: Comparison of kinetic data of binding of 3.0 mM bile acid salts**

| Time (min.) | Bound, mg | | | | | |
|---|---|---|---|---|---|---|
| | GC | | GCDC | | TDC | |
| | Oral Powder1 | Tablets | Oral Powder1 | Tablets | Oral Powder1 | Tablets |
| 3 | 178.5 | 186.6 | 290.0 | 292.9 | 114.9 | 115.1 |
| 6 | 205.2 | 219.0 | 319.2 | 325.2 | 123.6 | 124.7 |
| 9 | 215.7 | 230.5 | 328.9 | 333.9 | 126.0 | 127.0 |
| 12 | 220.6 | 235.3 | 333.0 | 338.0 | 127.2 | 128.0 |
| 15 | 223.5 | 237.9 | 335.4 | 340.3 | 127.8 | 128.3 |
| 30 | 228.5 | 241.7 | 340.0 | 344.3 | 129.0 | 129.5 |
| 60 | 230.0 | 243.0 | 342.6 | 346.4 | 129.7 | 130.4 |
| 120 | 229.7 | 243.7 | 344.2 | 347.7 | 130.4 | 130.9 |
| 240 | 227.6 | 240.0 | 345.2 | 348.1 | 130.5 | 131.0 |
| 480 | 225.3 | 238.5 | 345.5 | 348.7 | 130.5 | 131.1 |
| 960 | 222.8 | 236.4 | 345.5 | 348.6 | 130.5 | 131.1 |
| 1440 | 221.6 | 235.7 | 346.1 | 348.3 | 130.7 | 131.2 |

*Comments:* The binding at the initial 0.3 mM concentration was extremely rapid for both dosage forms. The results for both concentrations were extremely reproducible. Additionally, the kinetic binding of 0.3 mM and 3.0 mM bile salts for both dosage forms was nearly identical. Therefore, based on these data Welchol tablets and powder for oral suspension are comparable in terms of its *in vitro* binding characteristics.

## 2.4 Analytical

(b) (4)

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(H) 1 page of Biopharm withheld in full immediately following this page as B4 CCI/TS

## 3 Labeling Comments

The Office of Clinical Pharmacology (OCP/DCP-2) has reviewed the package insert labeling for Welchol and finds it acceptable.

## 4. Appendix

### 4.1 Proposed label

(I) 21 pages of Biopharm has been withheld in full immediately following this page as B4 CCI/TS

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