CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 090379

Name: Budesonide Capsules, 3 mg (Enteric Coated)

Sponsor: Barr Laboratories, Inc.

Approval Date: April 2, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 090379

Barr Laboratories, Inc.
Attention: Scott D. Tomsky
Vice President
Regulatory Affairs, North America, Generics
425 Privet Road
Horsham, PA 19044

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Budesonide Capsules, 3 mg (Enteric Coated).

Reference is also made to the Complete Response letter issued by this office on April 3, 2012, and to your amendments dated April 1, and April 12, 2013.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Budesonide Capsules, 3 mg (Enteric Coated), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Entocort EC Capsules, 3 mg, of AstraZeneca LP (AstraZeneca). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in:

Apparatus:	USP Apparatus 2 (paddle), with capsule sinker
Rotation speed:	75 rpm
Medium:	Acid stage: First 2 hours 0.1 N HCl Buffer stage: 1-6 hours

	Phosphate Buffer, pH 7.5
Volume:	1000 mL for both Acid Stage and Buffer Stage
Temperature:	37°C
Sampling times:	Acid Stage: 2 hours Buffer stage: 1, 2, 4 and 6 hours

The test product should meet the following "interim" specifications:

Acid Stage:	Time (hours)	% Budesonide Dissolved
	2	NMT (b) (4) %

Buffer Stage:	Time (hours)	% Budesonide Dissolved
	1	(b) (4) %
	2	%
	4	%
	6	NLT (b) (4) %

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Astra Zeneca's Entocort EC Capsules, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,643,602 (the '602 patent), is scheduled to expire on January 1, 2015 (with pediatric exclusivity extension added.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '602 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Budesonide Capsules, 3 mg, under this ANDA. You have notified the agency that Barr Laboratories, Inc. (Barr) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Barr for infringement of the '602 patent within the statutory 45-day period in the United States District Court for the District of Delaware [AstraZeneca LP, Aktiebolaget Draco, KBI Inc., and KBI-E Inc. v. Barr Laboratories, Inc., Civil

Action No. 08-305]. You have also notified the agency that this litigation has been dismissed.

With respect to 180-day generic drug exclusivity, we note that Barr was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Budesonide Capsules, 3 mg. As a first applicant, Barr was eligible for 180 days of generic drug exclusivity. The Agency has determined, however, that Barr forfeited its eligibility for 180-day exclusivity because Barr failed to obtain tentative approval within 30-months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the Act.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

04/02/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Budesonide capsules (enteric coated) safely and effectively. See full prescribing information for Budesonide capsules (enteric coated).

Budesonide capsules (enteric coated), for oral use Initial US Approval: 1997

------ INDICATIONS AND USAGE -----

Budesonide capsules (enteric coated) is a glucocorticosteroid indicated for:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. (1.1)
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months. (1.2)

--- DOSAGE AND ADMINISTRATION ---

- Mild to moderate active Crohn's disease: 9 mg once daily in the morning for up to 8 weeks. Repeated 8 week courses of budesonide capsules (enteric coated) can be given for recurring episodes of active disease. (2.1)
- Maintenance of clinical remission of mild to moderate Crohn's disease: 6 mg once daily for up to 3 months. Continued treatment with budesonide capsules (enteric coated) 6 mg for more than 3 months has not been shown to provide substantial clinical benefit. (2.2)

-- DOSAGE FORMS AND STRENGTHS --

Capsules: 3 mg (3)

--------- CONTRAINDICATIONS --------

Hypersensitivity to any of the ingredients in budesonide capsules (enteric coated). (4)

-- WARNINGS AND PRECAUTIONS --

- Hypercorticism and adrenal suppression: Since budesonide capsules (enteric coated) is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed. (5.1)
- Transferring patients from systemic glucocorticosteroid therapy: Care is needed in patients who are transferred from glucocorticosteroid treatment with high systemic effects to corticosteroids with lower systemic availability, such as budesonide capsules (enteric coated). (5.2)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.3)

-------- ADVERSE REACTIONS --------

Most common adverse reactions (≥ 5%) are headache, respiratory infection, nausea, back pain, dyspepsia, dizziness, abdominal pain, flatulence, vomiting, fatigue, pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-888-838 2872, X6351 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--------- DRUG INTERACTIONS --------

- Cytochrome P450 3A4 inhibitors (e.g., ketoconazole, grapefruit juice) should be avoided. May cause increased systemic corticosteroid effects. (2.3, 7, 12.3)

-- USE IN SPECIFIC POPULATIONS --

- Hepatic Insufficiency: Monitor patients for signs and/or symptoms of hypercorticism. (5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: December 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Mild to Moderate Active Crohn's Disease
- 1.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

2 DOSAGE AND ADMINISTRATION
- 2.1 Mild to Moderate Active Crohn's Disease
- 2.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease
- 2.3 CYP3A4 inhibitors

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Hypercorticism and Adrenal Suppression
- 5.2 Transferring Patients from Systemic Glucocorticosteroid Therapy
- 5.3 Immunosuppression
- 5.4 Increased Systemic Glucocorticosteroid Susceptibility
- 5.5 Other Glucocorticosteroid Effects

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Insufficiency

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
- 17.1 Hypercorticism and Adrenal Suppression
- 17.2 Immunosuppression
- 17.3 How to Take Budesonide Capsules (Enteric Coated)

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mild to Moderate Active Crohn's Disease

Budesonide capsules (enteric coated) is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

1.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

Budesonide capsules (enteric coated) is indicated for the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.

2 DOSAGE AND ADMINISTRATION

2.1 Mild to Moderate Active Crohn's Disease

The recommended adult dosage for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon is 9 mg orally taken once daily in the morning for up to 8 weeks. Repeated 8 week courses of budesonide capsules (enteric coated) can be given for recurring episodes of active disease.

2.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

Following an 8 week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI less than 150), budesonide capsules (enteric coated) 6 mg orally is recommended once daily for maintenance of clinical remission up to 3 months. If symptom control is still maintained at 3 months an attempt to taper to complete cessation is recommended. Continued treatment with budesonide capsules (enteric coated) 6 mg for more than 3 months has not been shown to provide substantial clinical benefit.

Patients with mild to moderate active Crohn's disease involving the ileum and/or ascending colon have been switched from oral prednisolone to budesonide capsules (enteric coated) with no reported episodes of adrenal insufficiency. Since prednisolone should not be stopped abruptly, tapering should begin concomitantly with initiating budesonide capsules (enteric coated) treatment.

2.3 CYP3A4 inhibitors

If concomitant administration with ketoconazole, or any other CYP3A4 inhibitor, is indicated, patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Grapefruit juice, which is known to inhibit CYP3A4, should also be avoided when taking budesonide capsules (enteric coated). In these cases, reduction in the dose of budesonide capsules (enteric coated) should be considered [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Budesonide capsules (enteric coated) 3 mg are elongated, two-piece hard gelatin capsules with dark peach opaque cap and white opaque body, filled with white to off-white pellets, imprinted with "TEVA 7445" in black ink, containing 3 mg budesonide.

4 CONTRAINDICATIONS

Budesonide capsules (enteric coated) is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of budesonide capsules (enteric coated). Anaphylactic reactions have occurred [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Suppression

When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since budesonide capsules (enteric coated) are a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.

5.2 Transferring Patients from Systemic Glucocorticosteroid Therapy

Care is needed in patients who are transferred from glucocorticosteroid treatment with high systemic effects to corticosteroids with lower systemic availability, such as budesonide capsules (enteric coated), since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously.

5.3 Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure.

How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered.

Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections.

Replacement of systemic glucocorticosteroids with budesonide capsules (enteric coated) capsules may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic drug.

5.4 Increased Systemic Glucocorticosteroid Susceptibility

Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis [*see Use in Specific Populations (8.6)*].

5.5 Other Glucocorticosteroid Effects

Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

Systemic glucocorticosteroid use may result in the following:

- Hypercorticism and Adrenal Suppression [*see Warnings and Precautions (5.1)*]
- Symptoms of steroid withdrawal in those patients transferring from Systemic Glucocorticosteroid Therapy [*see Warnings and Precautions (5.2)*]
- Immunosuppression [*see Warnings and Precautions (5.3)*]
- Increased Systemic Glucocorticosteroid Susceptibilty [*see Warnings and Precautions (5.4)*]
- Other Glucocorticosteroid Effects [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice

The safety of budesonide capsules (enteric coated) was evaluated in 651 patients in five short-term, active disease state studies. They ranged in age from 17 to 74 (mean 35), 40% were male and 97% were white, 2.6% were greater than or equal to 65 years of age. Five hundred and twenty patients were treated with budesonide capsules (enteric coated) 9 mg (total daily dose). The most common adverse reactions reported were headache, respiratory infection, nausea, and symptoms of hypercorticism. Clinical studies have shown that the frequency of glucocorticosteroid- associated adverse reactions was substantially reduced with budesonide capsules (enteric coated) compared with prednisolone at therapeutically equivalent doses. Adverse reactions occurring in greater than or equal to 5% of the patients are listed in **Table 1**:

Table 1 Adverse Reactions Occurring in greater than or equal to 5% of the Patients in any treated group

Adverse Reaction	Budesonide Capsules (enteric coated) 9 mg n = 520 Number (%)	Placebo n = 107 Number (%)	Prednisolone 40 mg n = 145 Number (%)	Comparator* n = 88 Number (%)
Headache	107(21)	19(18)	31(21)	11(13)
Respiratory Infection	55 (11)	7(7)	20(14)	5(6)
Nausea	57(11)	10(9)	18(12)	7(8)
Back Pain	36(7)	10(9)	17(12)	5(6)
Dyspepsia	31(6)	4(4)	17(12)	3(3)
Dizziness	38(7)	5(5)	18(12)	5(6)
Abdominal Pain	32(6)	18(17)	6(4)	10(11)
Flatulence	30(6)	6(6)	12(8)	5(6)
Vomiting	29(6)	6(6)	6(4)	6(7)
Fatigue	25(5)	8(7)	11(8)	0(0)
Pain	24(5)	8(7)	17(12)	2(2)

* This drug is not approved for the treatment of Crohn's disease in the United States.

The safety of budesonide capsules (enteric coated) was evaluated in 233 patients in four long-term clinical trials (52 weeks). A total of 145 patients were treated with budesonide capsules (enteric coated) 6 mg. A total of 8% of budesonide capsules (enteric coated) patients discontinued treatment due to adverse reactions compared with 10% in the placebo group. The adverse reaction profile in long-term treatment of Crohn's disease was similar to that of short-term treatment with budesonide capsules (enteric coated) 9 mg in active Crohn's disease.

In the long-term clinical trials, the following adverse reactions occurred in greater than or equal to 5% of the 6 mg budesonide capsules (enteric coated) patients and are not listed in (**Table 1**) or by body system below: diarrhea (10%); sinusitis (8%); infection viral (6%); and arthralgia (5%).

Adverse reactions, occurring in patients treated with budesonide capsules (enteric coated) 9 mg (total daily dose) in short-term active disease state studies and/or budesonide capsules (enteric coated) 6 mg (total daily dose) long-term, with an incidence less than 5% and greater than placebo are listed below by system organ class:

Blood and lymphatic system disorders: leukocytosis

Cardiac disorders: palpitation, tachycardia

Eye disorders: eye abnormality, vision abnormal

General disorders and administration site conditions: asthenia, chest pain, dependent edema, face edema, flu-like disorder, malaise, fever

Gastrointestinal disorders: anus disorder, Crohn's disease aggravated, enteritis, epigastric pain, gastrointestinal fistula, glossitis, hemorrhoids, intestinal obstruction, tongue edema, tooth disorder

Infections and infestations: Ear infection-not otherwise specified, bronchitis, abscess, rhinitis, urinary tract infection, thrush

Investigations: c-reactive protein increased, weight increased

Metabolism and nutrition disorders: appetite increased, hypokalemia

Musculoskeletal and connective tissue disorders: arthritis, cramps, myalgia

Nervous system disorders: hyperkinesia, parasthesia, tremor, vertigo, dizziness, somnolence, amnesia

Psychiatric disorders: agitation, confusion, insomnia, nervousness, sleep disorder

Renal and urinary disorders: dysuria, micturition frequency, nocturia

Reproductive system and breast disorders: intermenstrual bleeding, menstrual disorder

Respiratory, thoracic and mediastinal disorders: dyspnea, pharynx disorder

Skin and subcutaneous tissue disorders: acne, alopecia, dermatitis, eczema, skin disorder, sweating increased, purpura

Vascular disorders: flushing, hypertension

Table 2 displays the frequency and incidence of signs/symptoms of hypercorticism by active questioning of patients in short-term clinical trials.

Table 2 Summary and Incidence of Signs/Symptoms of Hypercorticism in Short-Term Studies

Signs/Symptoms	Budesonide Capsules (enteric coated) 9 mg n = 427 Number (%)	Placebo n = 107 Number (%)	Prednisolone Taper 40 mg n = 145 Number (%)
Acne	63(15)	14(13)	33(23)*
Bruising Easily	63(15)	12(11)	13(9)
Moon Face	46(11)	4(4)	53(37)*
Swollen Ankles	32(7)	6(6)	13(9)
Hirsutism†	22(5)	2(2)	5(3)
Buffalo Hump	6(1)	2(2)	5(3)
Skin Striae	4(1)	2(2)	0(0)

* Statistically significantly different from budesonide capsules (enteric coated) 9 mg

† Adverse reaction dictionary included term hair growth increased, local and hair growth increased, general.

Table 3 displays the frequency and incidence of signs/symptoms of hypercorticism by active questioning of patients in long-term clinical trials.

Table 3 Summary and Incidence of Symptoms of Hypercorticism in Long-Term Studies

Signs/Symptoms	Budesonide Capsules (enteric coated) 3 mg n = 88 Number (%)	Budesonide Capsules (enteric coated) 6 mg n = 145 Number (%)	Placebo n = 143 Number (%)
Bruising Easily	4(5)	15(10)	5(4)
Acne	4(5)	14(10)	3(2)
Moon Face	3(3)	6(4)	0
Hirsutism	2(2)	5(3)	1(1)
Swollen Ankles	2(2)	3(2)	3(2)
Buffalo Hump	1(1)	1(1)	0
Skin Striae	2(2)	0	0

The incidence of signs/symptoms of hypercorticism as described above in long-term clinical trials was similar to that seen in the short-term clinical trials.

A randomized, open, parallel-group multicenter safety study specifically compared the effect of budesonide capsules (enteric coated) (less than 9 mg per day) and prednisolone (less than 40 mg per day) on bone mineral density over 2 years when used at doses adjusted to disease severity. Bone mineral density decreased significantly less with budesonide capsules (enteric coated) than with prednisolone in steroid-naïve patients, whereas no difference could be detected between treatment groups for steroid-dependent patients and previous steroid users. The incidence of symptoms associated with hypercorticism was significantly higher with prednisolone treatment.

Clinical Laboratory Test Findings

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to budesonide capsules (enteric coated), were reported in greater than or equal to 1% of patients: hypokalemia, leukocytosis, anemia, hematuria, pyuria, erythrocyte sedimentation rate increased, alkaline phosphatase increased, atypical neutrophils, C-reactive protein increased, and adrenal insufficiency.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of budesonide capsules (enteric coated). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylactic reactions

Nervous System Disorders: Benign intracranial hypertension

Psychiatric Disorders: Mood swings

7 DRUG INTERACTIONS

Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, etc.) is indicated, reduction of the budesonide dose should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy category C

Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

8.3 Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum[1]. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum budesonide concentration for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after inhalation. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg per day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide plasma concentrations obtained from five infants at about 90 minutes after breast feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (less than 0.02 nmol/L in four infants and less than 0.04 nmol/L in one infant).

The recommended daily dose of budesonide capsules (enteric coated) is higher (up to 9 mg daily) compared with inhaled budesonide (up to 800 mcg daily) given to mothers in the above study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5 to 10 nmol/L which is up to 10 times higher than the 1 to 2 nmol/L for a 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study.

Since there are no data from controlled trials on the use of budesonide capsules (enteric coated) by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from budesonide capsules (enteric coated), a decision should be made whether to discontinue nursing or to discontinue budesonide capsules (enteric coated), taking into account the clinical importance of budesonide capsules (enteric coated) to the mother.

Budesonide is secreted in human milk. Data from budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of budesonide capsules (enteric coated), budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Systemic and inhaled corticosteroids, including budesonide capsules (enteric coated), may cause a reduction of growth velocity in pediatric patients.

8.5 Geriatric Use

Clinical studies of budesonide capsules (enteric coated) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

8.6 Hepatic Insufficiency

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Reducing the dose of budesonide capsules (enteric coated) should be considered in these patients [*see Warnings and Precautions (5.4)*].

10 OVERDOSAGE

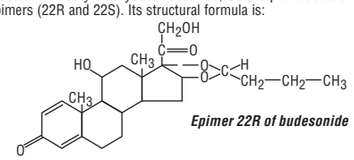
Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage may be reduced temporarily.

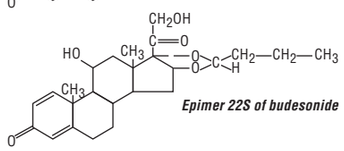
Single oral doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

11 DESCRIPTION

Budesonide, USP, the active ingredient of budesonide capsules (enteric coated), is a synthetic corticosteroid. Budesonide, USP is designated chemically as (RS)-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide, USP is provided as a mixture of two epimers (22R and 22S). Its structural formula is:



Epimer 22R of budesonide



Epimer 22S of budesonide

$C_{25}H_{34}O_6$ M.W. 430.5

Budesonide, USP is a white to off-white, tasteless, odorless powder that is practically insoluble in water and heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 5 is 1.6 x 10^3 ionic strength 0.01.

Each capsule for oral administration contains 3 mg of micronized budesonide, USP with the following inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose monohydrate, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate. The ingredients in the capsule shell are FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide. The ingredients in the imprinting ink are D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, shellac glaze, black iron oxide and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Budesonide has a high topical glucocorticosteroid (GCS) activity and a substantial first pass elimination. The formulation contains granules which are coated to protect dissolution in gastric juice, but which dissolve at pH greater than 5.5, i.e., normally when the granules reach the duodenum. Thereafter, a matrix of ethylcellulose with budesonide controls the release of the drug into the intestinal lumen in a time-dependent manner.

12.2 Pharmacodynamics

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to GCS receptors, which reflects the intrinsic potency of the drug, is about 200 fold that of cortisol and 15 fold that of prednisolone.

Treatment with systemically active GCS is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. Markers, indirect and direct, of this are cortisol levels in plasma or urine and response to ACTH stimulation.

Plasma cortisol suppression was compared following five days' administration of budesonide capsules (enteric coated) and prednisolone in a crossover study in healthy volunteers. The mean decrease in the integrated 0 to 24 hour plasma cortisol concentration was greater (78%) with prednisolone 20 mg per day compared to 45% with budesonide capsules (enteric coated) 9 mg per day.

12.3 Pharmacokinetics

Absorption

The absorption of budesonide capsules (enteric coated) seems to be complete, although C_{max} and T_{max} are variable. Time to peak concentration varies in individual patients between 30 and 600 minutes. Following oral administration of 9 mg of budesonide in healthy subjects, a peak plasma concentration of approximately 5 nmol/L is observed and the area under the plasma concentration time curve is approximately 30 nmol*hr/L. The systemic availability after a single dose is higher in patients with Crohn's disease compared to healthy volunteers, (21% vs 9%) but approaches that in healthy volunteers after repeated dosing.

Patient Information
Budesonide (bue des' oh nide)
Capsules (Enteric Coated)

Read the Patient Information that comes with budesonide capsules (enteric coated) before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What are Budesonide Capsules (Enteric Coated)?

Budesonide capsules (enteric coated) is a prescription glucocorticosteroid medicine used in people with mild to moderate Crohn's disease that affects part of the small intestine (ileum) and part of the large intestine (ascending colon):

- to treat active Crohn's disease
- to help keep symptoms from coming back for up to 3 months.

It is not known if budesonide capsules (enteric coated) is safe and effective in children.

Who should not take Budesonide Capsules (Enteric Coated)?

Do not take Budesonide Capsules (Enteric Coated) if:

- you are allergic to budesonide or any of the ingredients in budesonide capsules (enteric coated). See the end of this leaflet for a complete list of ingredients in budesonide capsules (enteric coated).

What should I tell my healthcare provider before taking Budesonide Capsules (Enteric Coated)?

Before you take Budesonide Capsules (Enteric Coated) tell your healthcare provider if you:

- have liver problems
- are planning to have surgery
- have chicken pox or measles or have recently been near anyone with chicken pox or measles
- have or had a family history of diabetes, cataracts or glaucoma
- have or had tuberculosis
- have high blood pressure (hypertension)
- have decreased bone mineral density (osteoporosis)
- stomach ulcers
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if budesonide capsules (enteric coated) may harm your unborn baby.
- are breastfeeding or plan to breastfeed. Budesonide capsules (enteric coated) can pass into breast milk and may harm your baby. You and your healthcare provider should decide if you will take budesonide capsules (enteric coated) or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Budesonide capsules (enteric coated) and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a glucocorticosteroid medicine
- medicines that suppress your immune system (immunosuppressant)
- ketoconazole or other medicines that affect how your liver works.

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one listed above.

How should I take Budesonide Capsules (Enteric Coated)?

- Take budesonide capsules (enteric coated) exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how many budesonide capsules (enteric coated) to take. Your healthcare provider may change your dose if needed.
- Take budesonide capsules (enteric coated) in the morning.
- Take budesonide capsules (enteric coated) whole. Do not chew or crush budesonide capsules (enteric coated) before swallowing.

What should I avoid while taking Budesonide Capsules (Enteric Coated)?

- Do not eat grapefruit or drink grapefruit juice while taking budesonide capsules (enteric coated). Eating grapefruit or drinking grapefruit juice can increase the level of budesonide capsules (enteric coated) in your blood.

What are the possible side effects of Budesonide Capsules (Enteric Coated)?

- **Effects of having too much glucocorticosteroid medicine in your blood (hypercorticism).** Long-time use of budesonide capsules (enteric coated) can cause you to have too much glucocorticosteroid medicine in your blood. Tell your healthcare provider if you have any of the following signs and symptoms of hypercorticism:
  - acne
  - bruise easily
  - rounding of your face (moon face)
  - ankle swelling
  - thicker or more hair on your body and face
  - a fatty pad or hump between your shoulders (buffalo hump)
  - pink or purple stretch marks on the skin of your abdomen, thighs, breasts and arms

799-33-100282

1 2 3 4 5 7 4 2 R

Iss. 12/2011

7445

BUDESONIDE CAPSULES (Enteric Coated)

Rx only

0862

Reference ID: 3294705

- **Adrenal suppression.** When budesonide capsules (enteric coated) is taken for a long period of time (chronic use), adrenal suppression can happen. This is a condition in which the adrenal glands do not make enough steroid hormones. Symptoms of adrenal suppression include: tiredness, weakness, nausea and vomiting and low blood pressure. Tell your healthcare provider if you are under stress or have any symptoms of adrenal suppression during treatment with budesonide capsules (enteric coated).
- **Immune system effects and a higher chance of infections.** Budesonide capsules (enteric coated) weakens your immune system. Taking medicines that weaken your immune system makes you more likely to get infections. Avoid contact with people who have contagious diseases such as chicken pox or measles, while taking budesonide capsules (enteric coated).

  Tell your healthcare provider about any signs or symptoms of infection during treatment with budesonide capsules (enteric coated), including:
  - fever
  - chills
  - pain
  - feeling tired
  - aches
  - nausea and vomiting
- **Worsening of allergies.** If you take certain other glucocorticosteroid medicines to treat allergies, switching to budesonide capsules (enteric coated) may cause your allergies to come back. These allergies may include eczema (a skin disease) or rhinitis (inflammation inside your nose). Tell your healthcare provider if any of your allergies become worse while taking budesonide capsules (enteric coated).

The most common side effects of budesonide capsules (enteric coated) include:
- headache
- infection in your air passages (respiratory infection)
- back pain
- upset stomach
- dizziness
- abdominal pain
- excessive stomach or intestinal gas
- diarrhea
- sinus infection
- viral infection
- joint pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of budesonide capsules (enteric coated). For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store Budesonide Capsules (Enteric Coated)?
- Store budesonide capsules (enteric coated) at 68°F to 77°F (20°C to 25°C).
- Keep budesonide capsules (enteric coated) in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Keep Budesonide Capsules (Enteric Coated) and all medicines out of reach from children.

General information about Budesonide Capsules (Enteric Coated).

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use budesonide capsules (enteric coated) for a condition for which it was not prescribed. Do not give budesonide capsules (enteric coated) to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about budesonide capsules (enteric coated). If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about budesonide capsules (enteric coated) that is written for health professionals.

For more information call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in Budesonide Capsules (Enteric Coated)?

Active ingredient: budesonide, USP

Inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose monohydrate, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate.

The capsule shell contains: FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide.

The ingredients in the imprinting ink contains: D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, shellac glaze, black iron oxide and propylene glycol.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Reference ID: 3294705

Iss. 12/2011

Distribution

The mean volume of distribution (V_{ss}) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is about 0.8.

Metabolism

Following absorption, budesonide is subject to high first pass metabolism (80 to 90%). *In vitro* experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (less than 1/100) in relation to that of the parent compound.

In vivo investigations with intravenous doses in healthy subjects are in agreement with the *in vitro* findings and demonstrate that budesonide has a high plasma clearance, 0.9 to 1.8 L/min. Similarly, high plasma clearance values have been shown in patients with Crohn's disease. These high plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

The plasma elimination half-life, $t_{1/2}$, after administration of intravenous doses ranges between 2 and 3.6 hours, and does not differ between healthy adults and patients with Crohn's disease.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^{3}H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

Special Populations

Gender

No significant pharmacokinetic differences have been identified due to gender.

Hepatic Insufficiency

In patients with liver cirrhosis, systemic availability of orally administered budesonide correlates with disease severity and is, on average, 2.5 fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the intravenous dose, no significant differences in CL or V_{ss} are observed.

Renal Insufficiency

The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renally excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide (less than 1/100).

Drug-Drug Interactions

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide several-fold. Coadministration of ketoconazole results in an eight-fold increase in AUC of budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels.

Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (i.e., ethinyl estradiol) [*see Drug Interactions (7)*].

Since the dissolution of the coating of budesonide capsules (enteric coated) is pH dependent (dissolves at pH greater than 5.5), the release properties and uptake of the compound may be altered after treatment with drugs that change the gastrointestinal pH. However, the gastric acid inhibitory drug omeprazole, 20 mg once daily does not affect the absorption or pharmacokinetics of budesonide capsules (enteric coated). When an uncoated oral formulation of budesonide is coadministered with a daily dose of cimetidine 1 g, a slight increase in the budesonide peak plasma concentration and rate of absorption occurs, resulting in significant cortisol suppression.

Food Effects

A mean delay in time to peak concentration of 2.5 hours is observed with the intake of a high-fat meal, with no significant differences in AUC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91 week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis).

Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation (TK $^{+/-}$) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test and the mouse micronucleus test.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

14 CLINICAL STUDIES

The safety and efficacy of budesonide capsules (enteric coated) were evaluated in 994 patients with mild to moderate active Crohn's disease of the ileum and/or ascending colon in 5 randomized and double-blind studies. The study patients ranged in age from 17 to 85 (mean 35), 40% were male and 97% were white. Of the 651 patients treated with budesonide capsules (enteric coated), 17 (2.6%) were greater than or equal to 65 years of age and none were greater than 74 years of age. The Crohn's Disease Activity Index (CDAI) was the main clinical assessment used for determining efficacy in these 5 studies. The CDAI is a validated index based on subjective aspects rated by the patient (frequency of liquid or very soft stools, abdominal pain rating and general well-being) and objective observations (number of extraintestinal symptoms, need for antidiarrheal drugs, presence of abdominal mass, body weight and hematocrit). Clinical improvement, defined as a CDAI score of less than or equal to 150 assessed after 8 weeks of treatment, was the primary efficacy variable in these 5 comparative efficacy studies of budesonide capsules (enteric coated). Safety assessments in these studies included monitoring of adverse reactions. A checklist of potential symptoms of hypercorticism was used.

One study (Study 1) compared the safety and efficacy of budesonide capsules (enteric coated) 9 mg daily in the morning to a comparator. At baseline, the median CDAI was 272. Budesonide capsules (enteric coated) 9 mg daily resulted in a significantly higher clinical improvement rate at Week 8 than the comparator. See **Table 4**.

Table 4 Clinical Improvement Rates (CDAI less than or equal to 150) After 8 weeks of Treatment

Clinical Study	Budesonide Capsules (enteric coated)		Comparator*	Placebo	Prednisolone
	9 mg Daily	4.5 mg Twice Daily			
1	62/91 (69%)		37/83 (45%)		
2		31/61 (51%)		13/64 (20%)	
3	38/79 (48%)	41/78 (53%)		13/40 (33%)	
4	35/58 (60%)	25/60 (42%)			35/58 (60%)
5	45/86 (52%)				56/85 (65%)

* This drug is not approved for the treatment of Crohn's disease in the United States.

Two placebo-controlled clinical trials (Studies 2 and 3) were conducted. Study 2 involved 258 patients and tested the effects of graded doses of budesonide capsules (enteric coated) (1.5 mg twice daily, 4.5 mg twice daily, or 7.5 mg twice daily) versus placebo. At baseline, the median CDAI was 290. The 3 mg per day dose level (data not shown) could not be differentiated from placebo. The 9 mg per day arm was statistically different from placebo (**Table 4**), while no additional benefit was seen when the daily budesonide capsules (enteric coated) dose was increased to 15 mg per day (data not shown). In Study 3, the median CDAI at baseline was 263. Neither 9 mg daily nor 4.5 mg twice daily budesonide capsules (enteric coated) dose levels was statistically different from placebo (**Table 4**).

Two clinical trials (Studies 4 and 5) compared budesonide capsules (enteric coated) with oral prednisolone (initial dose 40 mg per day). At baseline, the median CDAI was 277. Equal clinical improvement rates (60%) were seen in the budesonide capsules (enteric coated) 9 mg daily and the prednisolone groups in Study 4. In Study 5, 13% fewer patients in the budesonide capsules (enteric coated) group experienced clinical improvement than in the prednisolone group (no statistical difference) (**Table 4**).

The proportion of patients with normal plasma cortisol values (greater than 150 nmol/L) was significantly higher in the budesonide capsules (enteric coated) groups in both trials (60 to 66%) than in the prednisolone groups (26 to 28%) at Week 8.

The efficacy and safety of budesonide capsules (enteric coated) for maintenance of clinical remission were evaluated in four double-blind, placebo-controlled, 12 month trials in which 380 patients were randomized and treated once daily with 3 mg or 6 mg budesonide capsules (enteric coated) or placebo. Patients ranged in age from 18 to 73 (mean 37) years. Sixty percent of the patients were female and 99% were Caucasian. The mean CDAI at entry was 96. Among the four clinical trials, approximately 75% of the patients enrolled had exclusively ileal disease. Colonoscopy was not performed following treatment. Budesonide capsules (enteric coated) 6 mg per day prolonged the time to relapse, defined as an increase in CDAI of at least 60 units to a total score greater than 150 or withdrawal due to disease deterioration. The median time to relapse in the pooled population of the 4 studies was 154 days for patients taking placebo, and 268 days for patients taking budesonide capsules (enteric coated) 6 mg per day. Budesonide capsules (enteric coated) 6 mg per day reduced the proportion of patients with loss of symptom control relative to placebo in the pooled population for the 4 studies at 3 months (28% vs. 45% for placebo).

16 HOW SUPPLIED/STORAGE AND HANDLING

Budesonide Capsules (Enteric Coated), 3 mg are available as elongated, two-piece hard gelatin capsules with dark peach opaque cap and white opaque body, filled with white to off-white pellets, imprinted with "TEVA 7445" in black ink, containing 3 mg budesonide, packaged in bottles of 100 capsules.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

17 PATIENT COUNSELING INFORMATION

"See FDA-Approved Patient Labeling (Patient Information)"

Patients being treated with budesonide capsules (enteric coated) should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects. For proper use of budesonide capsules (enteric coated) and to attain maximum improvement, the patient should read and follow the accompanying *FDA-Approved Patient Labeling.*

17.1 Hypercorticism and Adrenal Suppression

Patients should be advised that budesonide capsules (enteric coated) may cause systemic glucocorticosteroid effects of hypercorticism and adrenal suppression. Patients should taper slowly from systemic glucocorticosteroids if transferring to budesonide capsules (enteric coated) [*see Warnings and Precautions (5.1) and (5.2)*].

17.2 Immunosuppression

Patients who are on immunosuppressant doses of glucocorticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections [*see Warnings and Precautions (5.3)*].

17.3 How to Take Budesonide Capsules (Enteric Coated)

Budesonide capsules (enteric coated) should be swallowed whole and NOT CHEWED OR BROKEN. Patients should be advised to avoid the consumption of grapefruit juice for the duration of their budesonide capsules (enteric coated) therapy.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2011

Patient Information
Budesonide (bue des' oh nide)
Capsules (Enteric Coated)

Read the Patient Information that comes with budesonide capsules (enteric coated) before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What are Budesonide Capsules (Enteric Coated)?

Budesonide capsules (enteric coated) is a prescription glucocorticosteroid medicine used in people with mild to moderate Crohn's disease that affects part of the small intestine (ileum) and part of the large intestine (ascending colon):
- to treat active Crohn's disease
- to help keep symptoms from coming back for up to 3 months.

It is not known if budesonide capsules (enteric coated) is safe and effective in children.

Who should not take Budesonide Capsules (Enteric Coated)?

Do not take Budesonide Capsules (Enteric Coated) if:
- you are allergic to budesonide or any of the ingredients in budesonide capsules (enteric coated). See the end of this leaflet for a complete list of ingredients in budesonide capsules (enteric coated).

What should I tell my healthcare provider before taking Budesonide Capsules (Enteric Coated)?

Before you take Budesonide Capsules (Enteric Coated) tell your healthcare provider if you:
- have liver problems
- are planning to have surgery
- have chicken pox or measles or have recently been near anyone with chicken pox or measles
- have or had a family history of diabetes, cataracts or glaucoma
- have or had tuberculosis
- have high blood pressure (hypertension)
- have decreased bone mineral density (osteoporosis)
- stomach ulcers
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if budesonide capsules (enteric coated) may harm your unborn baby.
- are breastfeeding or plan to breastfeed. Budesonide capsules (enteric coated) can pass into breast milk and may harm your baby. You and your healthcare provider should decide if you will take budesonide capsules (enteric coated) or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Budesonide capsules (enteric coated) and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:
- a glucocorticosteroid medicine
- medicines that suppress your immune system (immunosuppressant)
- ketoconazale or other medicines that affect how your liver works.

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one listed above.

How should I take Budesonide Capsules (Enteric Coated)?
- Take budesonide capsules (enteric coated) exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how many budesonide capsules (enteric coated) to take. Your healthcare provider may change your dose if needed.
- Take budesonide capsules (enteric coated) in the morning.
- Take budesonide capsules (enteric coated) whole. Do not chew or crush budesonide capsules (enteric coated) before swallowing.

What should I avoid while taking Budesonide Capsules (Enteric Coated)?
- Do not eat grapefruit or drink grapefruit juice while taking budesonide capsules (enteric coated). Eating grapefruit or drinking grapefruit juice can increase the level of budesonide capsules (enteric coated) in your blood.

What are the possible side effects of Budesonide Capsules (Enteric Coated)?
- **Effects of having too much glucocorticosteroid medicine in your blood (hypercorticism).** Long-time use of budesonide capsules (enteric coated) can cause you to have too much glucocorticosteroid medicine in your blood. Tell your healthcare provider if you have any of the following signs and symptoms of hypercorticism:
  - acne
  - bruise easily
  - rounding of your face (moon face)
  - ankle swelling
  - thicker or more hair on your body and face
  - a fatty pad or hump between your shoulders (buffalo hump)
  - pink or purple stretch marks on the skin of your abdomen, thighs, breasts and arms
- **Adrenal suppression.** When budesonide capsules (enteric coated) is taken for a long period of time (chronic use), adrenal suppression can happen. This is a condition in which the adrenal glands do not make enough steroid hormones. Symptoms of adrenal suppression include: tiredness, weakness, nausea and vomiting and low blood pressure. Tell your healthcare provider if you are under stress or have any symptoms of adrenal suppression during treatment with budesonide capsules (enteric coated).
- **Immune system effects and a higher chance of infections.** Budesonide capsules (enteric coated) weakens your immune system. Taking medicines that weaken your immune system makes you more likely to get infections. Avoid contact with people who have contagious diseases such as chicken pox or measles, while taking budesonide capsules (enteric coated).

  Tell your healthcare provider about any signs or symptoms of infection during treatment with budesonide capsules (enteric coated), including:
  - fever
  - chills
  - pain
  - feeling tired
  - aches
  - nausea and vomiting
- **Worsening of allergies.** If you take certain other glucocorticosteroid medicines to treat allergies, switching to budesonide capsules (enteric coated) may cause your allergies to come back. These allergies may include eczema (a skin disease) or rhinitis (inflammation inside your nose). Tell your healthcare provider if any of your allergies become worse while taking budesonide capsules (enteric coated).

The most common side effects of budesonide capsules (enteric coated) include:
- headache
- infection in your air passages (respiratory infection)
- back pain
- upset stomach
- dizziness
- abdominal pain
- excessive stomach or intestinal gas
- diarrhea
- sinus infection
- viral infection
- joint pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of budesonide capsules (enteric coated). For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store Budesonide Capsules (Enteric Coated)?
- Store budesonide capsules (enteric coated) at 68°F to 77°F (20°C to 25°C).
- Keep budesonide capsules (enteric coated) in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Keep Budesonide Capsules (Enteric Coated) and all medicines out of reach from children.

General information about Budesonide Capsules (Enteric Coated).

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use budesonide capsules (enteric coated) for a condition for which it was not prescribed. Do not give budesonide capsules (enteric coated) to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about budesonide capsules (enteric coated). If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about budesonide capsules (enteric coated) that is written for health professionals.

For more information call 1-888-838-2872, MEDICAL AFFAIRS.

What are the ingredients in Budesonide Capsules (Enteric Coated)?

Active ingredient: budesonide, USP

Inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose monohydrate, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate.

The capsule shell contains: FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide.

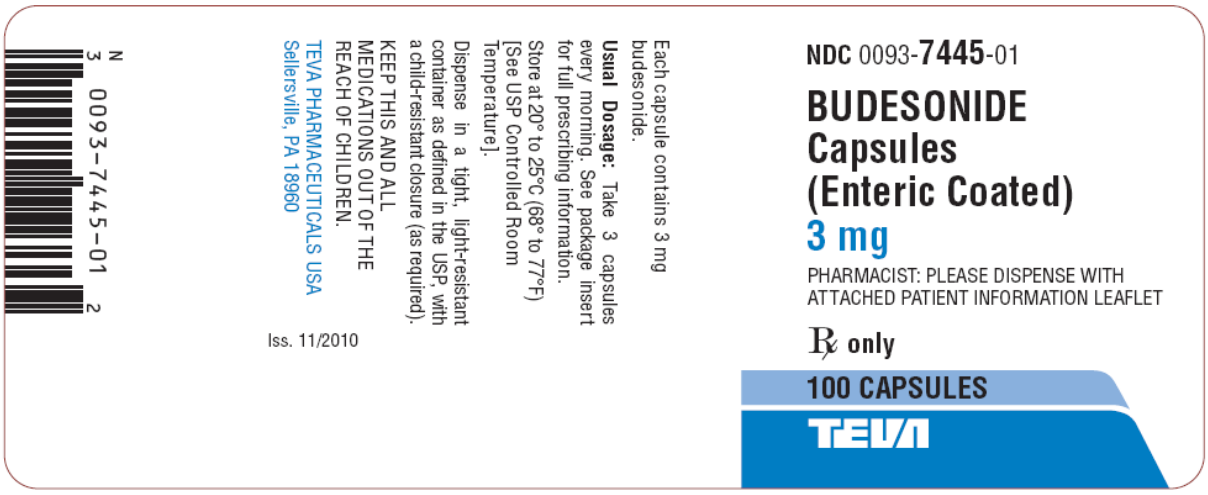
The ingredients in the imprinting ink contains: D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, shellac glaze, black iron oxide and propylene glycol.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Iss. 12/2011

ANDA 090379
Budesonide Capsules, 3 mg Enteric Coated

1.14.1 Final Printed Labeling



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

LABELING REVIEWS

LABELING APPROVAL SUMMARY #3
(Supersedes AP SUM dated 1/19/2011)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90379 Dates of Submission: February 1, 2012 and April 12, 2013

Applicant's Name: Barr Laboratories, Inc. (subsidiary of TEVA Pharmaceuticals USA)

Established Name: Budesonide Enteric Coated Capsules

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☐ Easily correctable (respond within 10 business days)

☒ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated February 1, 2012.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER (100's)
Satisfactory in FPL, January 7, 2011

PACKAGE INSERT
Satisfactory in FPL, February 1, 2012

PATIENT INFORMATION/ INSTRUCTIONS [Font size is 8 font]
Satisfactory in FPL, February 1, 2012

Revisions needed post-approval: Yes, we encourage you to increase the font size of the Patient Information Leaflet to size 8 font.

BASIS OF APPROVAL:
Was this approval based upon a petition?
What is the RLD on the 356(h) form:
NDA Number: 021234
NDA Drug Name: Entecort EC
NDA Firm: Astra Zeneca Pharmaceuticals LP
Date of Approval of NDA Insert and supplement #:021234/S-009, approved December 20, 2011
Was this approval based upon an OGD labeling guidance? No
Other Comments

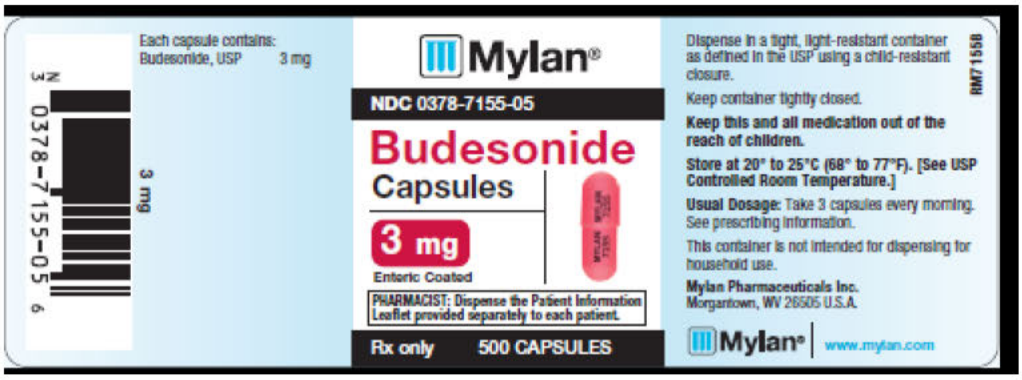
COMMENTS FROM CHEMIST/MICROBIOLOGIST/BIO REVIEWERS

FOR THE RECORD:

1. Labeling model
   Review based on the labeling of Astra Zeneca's "Entecort EC", (NDA 021324/S-011, approved, December 20, 2011). S-011 provides for PLR labeling.

   RLD container labels:

Approved generic is Mylan's 90410



2. USP/NF (Checked on April 16, 2013): Only the **DS** is compendial

PACKAGING AND STORAGE: Preserve in tight, light-resistant containers. Store at controlled room temperature.

3. MEDWATCH: No mention (checked on April 16, 2013)

4. Patent/ Exclusivities

Patent Data

Patent No	Patent Expiration	Use Code	Description	File	Impact
5643602*PED	Jan 1, 2015	U-655	TREATMENT OF MILD TO MODERATE ACTIVE CHROHN'S DISEASE INVOLVING THE ILEUM AND/OR THE ASCENDING COLON AND THE MAINTENANCE OF CLINICAL REMISSION OF MILD TO MODERATE CROHN'S DISEASE INVOLVING THE ILEUM AND/OR ASCENDING COLON FOR UP TO 3 MONTHS	IV	None

Exclusivity Data: There is no unexpired exclusivity for this product.

5. Inactive Ingredients: [C. Hoppes; review dated 1/19/2011]

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg]

ANDA: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate. The ingredients in the capsule shell are FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide. The ingredients in the imprinting ink are D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, iron oxide black and propylene glycol.

RLD: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have the following inactive ingredients: gelatin, iron oxide, and titanium dioxide

6. Manufacturing Facility [cover letter, 4/12/2012]
Barr Laboratories, Inc.
Woodcliff Lake, NJ 07677

7. **Product description** [C. Hoppes; review dated 1/19/2011]

RLD: ENTOCORT EC 3 mg capsules are hard gelatin capsules with an opaque light grey body and an opaque pink cap, coded with ENTOCORT EC 3 mg on the capsule and are supplied as follows: NDC 65483-702-10 Bottles of 100

ANDA: From HOW SUPPLIED

Budesonide Capsules (Enteric Coated), 3 mg are available as elongated, two-piece hard gelatin capsules with dark peach opaque cap and white opaque body, filled with white to off-white pellets, imprinted with "TEVA 7445" in black ink, containing 3 mg budesonide, packaged in bottles of 100 capsules.

8. **Container/Closure** [Chemist Review #4]
Barr's product is packaged in [redacted] (b) (4) 225 cc (100 count) HDPE bottles with plastic [redacted] (b) (4) 45 mm (100 count) CRC caps along with a [redacted] (b) (4)

9. Package Sizes
RLD: Bottles of 100s

ANDA: Bottles of 100s

10. Storage, Packaging and/or Dispensing:
NDA – Store at 25°C (77°F); excursions permitted to 15-30°C (5986°F) [See USP Controlled Room Temperature]. Keep container tightly closed.

ANDA : Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

11. Sister applications: None

12. SPL: DLDE acceptable in February 1, 2012, capsule size is 19 mm. Per Chemist review, size of capsule is Size #1 (which corresponds to length of 19 mm x diameter of 6.63 mm).

13. This ANDA container/carton labels:

Date of Review: April 16, 2013 Dates of Submission: February 1, 2012 and April 12, 2013

Primary Reviewer: Thuyanh (Ann) Vu Team Leader: John Grace

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

/s/

THUYANH VU
04/17/2013

JOHN F GRACE
04/17/2013

REVIEW OF PROFESSIONAL LABELING
APPROVAL SUMMARY - SUPERSEDES APPROVAL SUMMARY DATED MAY 15, 2009
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 090379 Date of Submission: January 7, 2011

Applicant's Name: TEVA Pharmaceuticals

Established Name: Budesonide Capsules, 3 mg

BASIS OF APPROVAL:
APPROVAL SUMMARY

REMS required?

MedGuides and/or PPIs (505-1(e))	☐ Yes **X** No
Communication plan (505-1(e))	☐ Yes ☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes ☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes ☐ No
Timetable for assessment (505-1(d))	☐ Yes ☐ No

ANDA REMS acceptable?
☐ Yes ☐ No **X** n/a

CONTAINER LABEL (3 mg: 100's):
Satisfactory in FPL, January 7, 2011

PACKAGE INSERT:
Satisfactory in FPL, January 7, 2011

PATIENT INFORMATION:
Satisfactory in FPL, January 7, 2011

FUTURE REVISIONS:
None Identified

BASIS OF APPROVAL:
Was this approval based upon a petition?
What is the RLD on the 356(h) form:
NDA Number: 021234
NDA Drug Name: Entecort EC
NDA Firm: Astra Zeneca Pharmaceuticals LP
Date of Approval of NDA Insert and supplement #:021234/S-008, approved June 22, 2009
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Other Comments

FOR THE RECORD (Some taken from previous review – a Labeling AS was completed on May 15, 2009):

1. Review based on the labeling of Astra Zeneca's "Entecort EC", NDA 021234/S-008, approved, June 22, 2009.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021324 Product 001 in the OB_Rx list.

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021324	001	5643602	Jul 1, 2014			U - 655	
N021324	001	5643602*PED	Jan 1, 2015		Y		
N021324	001	6423340	Nov 15, 2010				
N021324	001	6423340*PED	May 15, 2011				

There is no unexpired exclusivity for this product.

REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5643602	Jul 1, 2014 Jan 1, 2015 ped	U-655	TREATMENT OF MILD TO MODERATE ACTIVE CHROHN'S DISEASE INVOLVING THE ILEUM AND/OR THE ASCENDING COLON AND THE MAINTENANCE OF CLINICAL REMISSION OF MILD TO MODERATE CROHN'S DISEASE INVOLVING THE ILEUM AND/OR ASCENDING COLON FOR UP TO 3 MONTHS	PIV	Same
6423340	Nov 15, 2010 May 15, 2011			PIV	Same

Exclusivity Data For NDA

Code/sup	Expiration	Description	*Labeling impact*
None			

With TEVA's acquisition of Barr Laboratories, labeling submitted in the January 2011 submission has been revised accordingly.

2. MANUFACTURING FACILITY

Barr Laboratories in NJ.

3. STORAGE CONDITIONS/DISPENSING RECOMMENDATIONS/COMPATIBILITY:

RLD dispense it tight, light resistant….store at 25C (77F); excursion permitted to 15-30…

ANDA: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

USP: No monograph

4. INACTIVE INGREDIENTS:

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg]

ANDA: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate. The ingredients in the capsule shell are FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide. The ingredients in the imprinting ink are D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, iron oxide black and propylene glycol.

RLD: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have the following inactive ingredients: gelatin, iron oxide, and titanium dioxide

5. PACKAGING CONFIGURATIONS:

RLD: 100's

ANDA: (b) (4) 100's, at time of last approval summary, 100's at time of present review.

HOW SUPPLIED

Budesonide Capsules (Enteric Coated), 3 mg are available as elongated, two-piece hard gelatin capsules with dark peach opaque cap and white opaque body, filled with white to off-white pellets, imprinted with "TEVA 7445" in black ink, containing 3 mg budesonide, packaged in bottles of 100 capsules.

6. Imprint –
HOW SUPPLIED - Consistent with SPL data elements.

ANDA Capsule description:

HOW SUPPLIED

Budesonide Capsules (Enteric Coated), 3 mg are available as elongated, two-piece hard gelatin capsules with dark peach opaque cap and white opaque body, filled with white to off-white pellets, imprinted with "TEVA 7445" in black ink, containing 3 mg budesonide, packaged in bottles of 100 capsules.

(b) (4)

Following this page, 7 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

CHARLES V HOPPES
01/13/2011

JOHN F GRACE
01/19/2011

APPROVALSUMMARY #1
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-379
Que Date of Submission	28 APR 2009
Applicant	Barr
Drug Name	Budesonide Capsule, enteric coated
Strength(s)	3 mg

Labels and Labeling Summary	
Container	(b) (4) 100s- Satisfactory in FPL 28 APR 2009 \\Fdswa150\nonectd\N90379\N_000\2009-04-28\Module 1.14\1.14.1.1 Final Printed Container Labels.pdf
Patient leaflet	Satisfactory in FPL 28 APR 2009 \\Fdswa150\nonectd\N90379\N_000\2009-04-28\Module 1.14\1.14.1.3 Final Printed Patient Insert.pdf
Insert	Satisfactory in FPL on 28 APR 2009 \\Fdswa150\nonectd\N90379\N_000\2009-04-28\Module 1.14\1.14.1.3 Final Printed Package Insert.pdf

2. NOTE TO CHEMIST: Product has iron and yellow no.6

3. MODEL LABELING- This review was based on the labeling for the RLD. (b) (4)

Reference Listed Drug	
RLD on the 356(h) form	Entocort EC
NDA Number	21-324
RLD established name	Budesonide enteric coated capsule
Firm	AstraZeneca
Currently approved PI	SE-005
AP Date	Apr. 29, 2005
Note: RLD has one pending supplement -008	

4. PATENTS/EXCLUSIVITIES: See above [Vol. A1.1] REFERENCE LISTED DRUG:

REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5643602	Jul 1, 2014 Jan 1, 2015 ped	U-655	TREATMENT OF MILD TO MODERATE ACTIVE CHROHN'S DISEASE INVOLVING THE ILEUM AND/OR THE ASCENDING COLON AND THE MAINTENANCE OF CLINICAL REMISSION OF MILD TO MODERATE CROHN'S DISEASE INVOLVING THE ILEUM AND/OR ASCENDING COLON FOR UP TO 3 MONTHS	PIV	Same
6423340	Nov 15, 2010 May 15, 2011			PIV	Same

Exclusivity Data For NDA

Code/sup	Expiration	Description	*Labeling impact*
None			

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM by Barr Laboratories in NJ.

6. Packaging/CONTAINER/CLOSURE

RLD: 100s
NDA: (b) (4) 100s

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg]

ANDA: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate. The ingredients in the capsule shell are FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide. The ingredients in the imprinting ink are D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, iron oxide black and propylene glycol.

RLD: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have the following inactive ingredients: gelatin, iron oxide, and titanium dioxide

8. DISPENSING AND STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None
RLD: dispense it tight, light resistant….store at 25C (77F); excursion permitted to 15-30…
ANDA: Store at 20-25c…

9. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 5/13/09 Date of Submission: 28 APR 2009
Primary Reviewer: Angela Payne Date:
Team Leader: John Grace Date:

---

cc:

ANDA: 90-379
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:\FIRMSAM\Barr\LTRS&REV\90379na1labdfsreview.doc

Following this page, 7 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

Angela Payne
5/14/2009 11:46:47 AM
LABELING REVIEWER

John Grace
5/15/2009 11:13:12 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-379 Date of Submission: 31 Jan 2008

Applicant's Name: Barr Laboratories

Established Name: Budesonide Capsules 3 mg, Enteric Coated

Labeling Deficiencies:

1. **CONTAINER** ((b) (4) 100s): (b) (4)
   Revise (b) (4) to read "package insert". Place "enteric coated" low on the main panel.

2. **INSERT:** Where "Entocort EC" is used in the labeling of the reference listed drug, please use "budesonide capsules (enteric coated)". Using this designation is important since the labeling also talks about uncoated oral formulation of budesonide with another product results in significant cortisol suppression. In addition, specify the source of lactose in the Description section.

3. **PATIENT LEAFLET-** See comment under insert. Also, in accordance with the requirements for a toll-free number for the reporting of adverse events, we encourage you to include the following text at the end of the Patient Information:

   Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088.

Revise your lables and labeling, as instructed above, and submit final printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous submission with all differences annotated and explained.

FOR THE RECORD
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-379
Que Date of Submission	
Applicant	Barr
Drug Name	Budesonide Capsule, enteric coated
Strength(s)	3 mg

Labels and Labeling Summary	
Container	(b) (4) 100s
Patient leaflet Insert	

2. NOTE TO CHEMIST: Product has iron and yellow no.6

3. MODEL LABELING- This review was based on the labeling for the RLD. (b) (4)

Reference Listed Drug	
RLD on the 356(h) form	Entocort EC
NDA Number	21-324
RLD established name	Budesonide enteric coated capsule
Firm	AstraZeneca
Currently approved PI	SE-005
AP Date	Apr. 29, 2005
Note: RLD has one pending supplement -008	

4. PATENTS/EXCLUSIVITIES: See above [Vol. A1.1] REFERENCE LISTED DRUG:

REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5643602	Jul 1, 2014 Jan 1, 2015 ped	U-655	TREATMENT OF MILD TO MODERATE ACTIVE CHROHN'S DISEASE INVOLVING THE ILEUM AND/OR THE ASCENDING COLON AND THE MAINTENANCE OF CLINICAL REMISSION OF MILD TO MODERATE CROHN'S DISEASE INVOLVING THE ILEUM AND/OR ASCENDING COLON FOR UP TO 3 MONTHS	PIV	Same
6423340	Nov 15, 2010 May 15, 2011			PIV	Same

Exclusivity Data For NDA

Code/sup	Expiration	Description	*Labeling impact*
None			

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM by Barr Laboratories in NJ.

6. Packaging/CONTAINER/CLOSURE

RLD: 100s
NDA: (b) (4) 100s

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.1 pg]

ANDA: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: acetyltributyl citrate, ethylcellulose aqueous dispersion, glacial acetic acid, lactose, methacrylic acid copolymer dispersion, polysorbate 80, simethicone, sodium hydroxide, sugar spheres, talc and triethyl citrate. The ingredients in the capsule shell are FD&C yellow no. 6, FD&C red no. 40, gelatin and titanium dioxide. The ingredients in the imprinting ink are D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, iron oxide black and propylene glycol.

RLD: Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have the following inactive ingredients: gelatin, iron oxide, and titanium dioxide

8. DISPENSING AND STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None
RLD: dispense it tight, light resistant….store at 25C (77F); excursion permitted to 15-30…
ANDA: Store at 20-25c…

9. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 3/04/09 Date of Submission: 14 NOV 2008 and 17 FEB 2009
Primary Reviewer: Angela Payne Date:
Team Leader: John Grace Date:

---

cc:

ANDA: 90-379
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:\FIRMSAM\Barr\LTRS&REV\90379na1labdfsreview.doc

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

/s/

Angela Payne
3/6/2009 10:38:16 AM
LABELING REVIEWER

John Grace
3/12/2009 06:41:32 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

CHEMISTRY REVIEWS

ANDA 90379

Budesonide Enteric Coated Capsules

Teva Pharmaceuticals USA Inc.

Quamrul Majumder, Ph.D.

Office of Generic Drugs
Division of Chemistry II

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 3
The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

Chemistry Review Data Sheet

1. ANDA 90-379

2. REVIEW #: 5

3. REVIEW DATE: June 26, 2013

4. REVIEWER: Quameul Majumder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2008
Amendment	April 1, 2009
Amendment	September 22, 2009
Amendment	November 2, 2009
Amendment	April 23, 2010
Amendment	October 28, 2010
T-con Amendment (in-process testing chart)	November 8, 2010
Samples sent in Response to Info Request	March 28, 2011
T-con Amendment (information request)	March 30, 2011
Amendment –commitment	May 27, 2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment –commitment	April 12, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA Inc

Address: 400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Representative: Robert S. Vincent

Telephone: 201-930-3610

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Budesonide Enteric Coated Capsules

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject ANDA is the reference listed drug, Entocort® EC (NDA 21-324), manufactured by Astra Zeneca.

10. PHARMACOL. CATEGORY: Budesonide is indicated for the treatment of the signs and symptoms of Crohns Disease.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

15b. NANO TECHNOLOGY:

_____NANO product – Form Completed

__X__Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature: 16α,17-[(1RS)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (Technical Package)

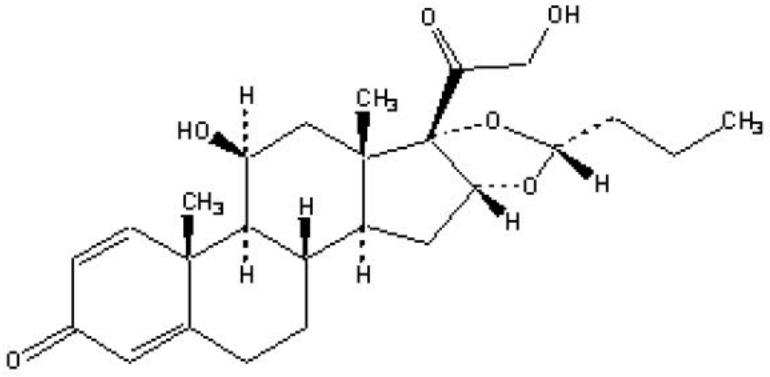
(RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (Technical Package, USP)
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(R)] (USP)
16α,17-[(S)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (USP)

CAS #: [51372-29-3; 51372-28-2; 51333-22-3]

USAN: Budesonide

Molecular Structure:

Mixture of epimer A and epimer B



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	IR letter	6/10/2013	M. Darj*

* (b) (4) Mike and Larry Lee e mailed Karen that the dmf review with IR status will not impact other dosage forms.

**Other DMFs for (b) (4) are cited but enough information was provided in ANDA so they were not reviewed or used in the review.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not Applicable		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Pending	4/11/13	
Methods Validation	Not Applicable		
Labeling	Acceptable	04/17/2013	VU, THUYANH
Bioequivalence	Acceptable	08/10/2011	MANDULA, HARITHA
EA	Not Applicable (category exclusion)		

Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-379

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective the application is now recommended for approval. The firm provided all of the updated information requested to provide assurance that the [(b) (4)] is controllable and reproducible. In addition the firm provided early validation batch data with respect to [(b) (4)] Finally as requested, the firm provided a commitment for future batches. See below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The firm submitted a commitment in their 5/27/11 amendment as requested that that stated that [(b) (4)] they will submit a Prior Approval Supplement to the Agency. [(b) (4)]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Budesonide is a white to off-white [(b) (4)] powder. It is practically insoluble in water and heptane and freely soluble in chloroform. [(b) (4)] [(b) (4)]. It is a mixture of 2 epimers A and B. It is the subject of USP and EP monographs The drug product is an orally administered capsule with a maximum daily dosage of 9 mg (3 x 3mg). It is an enteric coated (delayed release) formulation. It is supplied in HDPE bottles of [(b) (4)] 100 .

1) Description of How the Drug Product is Intended to be Used

Budesonide Capsules are used for Crohns Disease. The maximum daily dosage for Budesonide is 9 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is now recommended for approval, if EES is acceptable.

Following this page, 2 Pages Withheld in Full as (b)(4)

cc: ANDA 090379
ANDA DUP
DIV FILE
Field Copy

Endorsements :

HFD-640/QMajumder/ 6/26/2013
HFD-640/RRajagopalan/6/27/2013 – approval pending satisfactory EES
HFD-617/FNice/9/23/13

APPROVABLE

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

/s/

QUAMRUL MAJUMDER
09/23/2013

FRANK J NICE
09/23/2013

RADHIKA RAJAGOPALAN
09/23/2013

GLEN J SMITH
09/23/2013

ANDA 90379

Budesonide Enteric Coated Capsules

Teva Pharmaceuticals USA Inc.

Karen A. Bernard, Ph.D.

Office of Generic Drugs
Division of Chemistry II

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 3
The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

Chemistry Review Data Sheet

1. ANDA 90-379

2. REVIEW #: 4a-(ADDENDUM TO REVIEW #4)

3. REVIEW DATE: June 6, 2011

4. REVIEWER: Karen Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2008
Amendment	April 1, 2009
Amendment	September 22, 2009
Amendment	November 2, 2009
Amendment	April 23, 2010
Amendment	October 28, 2010
T-con Amendment (in-process testing chart)	November 8, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Samples sent in Response to Info Request	March 28, 2011
T-con Amendment (information request)	March 30, 2011
Amendment -commitment	May 27, 2011

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA Inc

Chemistry Review Data Sheet

Address: 400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Representative: Robert S. Vincent

Telephone: 201-930-3610

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Budesonide Enteric Coated Capsules

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject ANDA is the reference listed drug, Entocort® EC (NDA 21-324), manufactured by Astra Zeneca.

10. PHARMACOL. CATEGORY: Budesonide is indicated for the treatment of the signs and symptoms of Crohns Disease.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

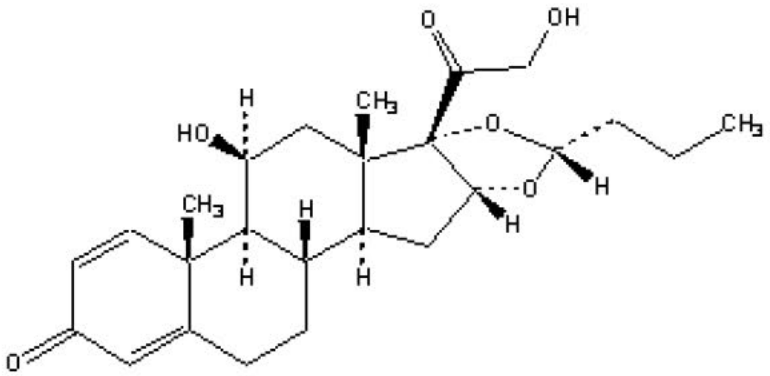
Nomenclature: 16α,17-[(1RS)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (Technical Package)
(RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (Technical Package, USP)
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(R)] (USP)
16α,17-[(S)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (USP)

CAS #: [51372-29-3; 51372-28-2; 51333-22-3]

USAN: Budesonide

Molecular Structure:

Mixture of epimer A and epimer B



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	6/15/2011	Review by K. Bernard

**Other DMFs for (b) (4) are cited but enough information was provided in ANDA so they were not reviewed or used in the review.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not Applicable		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	6/16/08	FJNice
Methods Validation	Not Applicable		
Labeling	Acceptable	5/15/09	A. Payne
Bioequivalence	Acceptable	3/5/09	O. Anand
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-379

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective the application is now recommended for approval. The firm provided all of the updated information requested to provide assurance that the [redacted] (b) (4) is controllable and reproducible. In addition the firm provided early validation batch data with respect to [redacted] (b) (4) Finally as requested, the firm provided a commitment for future batches. See below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The firm submitted a commitment in their 5/27/11 amendment as requested that that stated that [redacted] (b) (4) they will submit a Prior Approval Supplement to the Agency. [redacted] (b) (4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Budesonide is a white to off-white [redacted] (b) (4) powder. It is practically insoluble in water and heptane and freely soluble in chloroform. [redacted] (b) (4) [redacted] (b) (4). It is a mixture of 2 epimers A and B. It is the subject of USP and EP monographs The drug product is an orally administered capsule with a maximum daily dosage of 9 mg (3 x 3mg). It is supplied in HDPE bottles of [redacted] (b) (4) 100 .

1) Description of How the Drug Product is Intended to be Used

Budesonide Capsules are used for Crohns Disease. The maximum daily dosage for Budesonide is 9 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is now recommended for approval.

cc: ANDA 90-379
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 6/7/11;6/15/2011
HFD-640/RRajagopalan/6/13/2011;6/15/2011
HFD-617/FNice/6/15/11

F/T by:

V:\Firmsam\barr\Ltrs&Rev\90-379c4a

APPROVABLE

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

/s/

KAREN A BERNARD
06/15/2011

RADHIKA RAJAGOPALAN
06/15/2011

FRANK J NICE
06/16/2011

ANDA 90379

Budesonide Enteric Coated Capsules

Teva Pharmaceuticals USA Inc.

Karen A. Bernard, Ph.D.

Office of Generic Drugs
Division of Chemistry II

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 3
The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

Chemistry Review Data Sheet

1. ANDA 90-379

2. REVIEW #: 4

3. REVIEW DATE: November 9, 2010

4. REVIEWER: Karen Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2008
Amendment	April 1, 2009
Amendment	September 22, 2009
Amendment	November 2, 2009
Amendment	April 23, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	October 28, 2010
T-con Amendment (in-process testing chart)	November 8, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA Inc

Address: 400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Representative: Robert S. Vincent

Telephone: 201-930-3610

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Budesonide Enteric Coated Capsules

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject ANDA is the reference listed drug, Entocort® EC (NDA 21-324), manufactured by Astra Zeneca.

10. PHARMACOL. CATEGORY: Budesonide is indicated for the treatment of the signs and symptoms of Crohns Disease.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature: 16α,17-[(1RS)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (Technical Package)
(RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (Technical Package, USP)

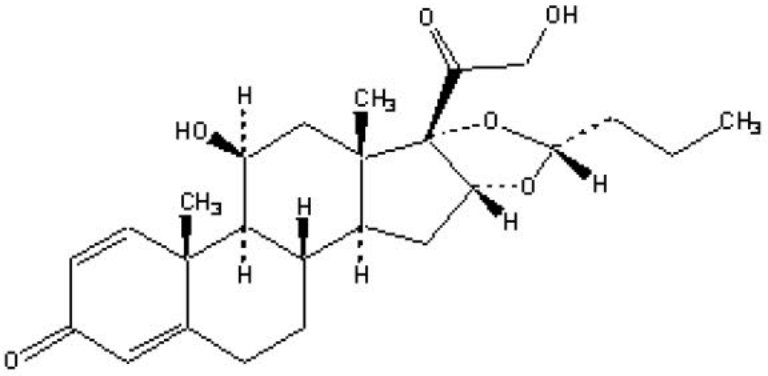
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(R)] (USP)
16α,17-[(S)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (USP)

CAS #: [51372-29-3; 51372-28-2; 51333-22-3]

USAN: Budesonide

Molecular Structure:

Mixture of epimer A and epimer B



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	11/9/10	Review by K. Bernard

**Other DMFs for (b) (4) are cited but enough information was provided in ANDA so they were not reviewed or used in the review.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not Applicable		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	6/16/08	FJNice
Methods Validation	Not Applicable		
Labeling	Acceptable	5/15/09	A. Payne
Bioequivalence	Acceptable	3/5/09	O. Anand
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-379

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective the application is now recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Budesonide is a white to off-white (b) (4) powder. It is practically insoluble in water and heptane and freely soluble in chloroform. (b) (4) (b) (4) It is a mixture of 2 epimers A and B. It is the subject of USP and EP monographs The drug product is an orally administered capsule with a maximum daily dosage of 9 mg (3 x 3mg). It is supplied in HDPE bottles of (b) (4) 100 .

1) Description of How the Drug Product is Intended to be Used

Budesonide Capsules are used for Crohns Disease. The maximum daily dosage for Budesonide is 9 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is now recommended for approval.

Following this page, 72 Pages Withheld in Full as (b)(4)

R REGIONAL INFORMATION

R.3.S Method Validation Package – Provided in appropriate section (M3)

R.1.P.1 Executed Batch Records – Provided in appropriate section (M3)

R.1.P.2 Information on Components – Provided in appropriate section (M3)

R.2.P Comparability Protocols - Not applicable.

R.3.P Methods Validation Package – Provided in appropriate section (M3)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert - From chemistry's perspective information in the description and how supplied sections of the package insert corresponds with information provided in the application.

B. Environmental Assessment Or Claim Of Categorical Exclusion - The applicant requests a categorical exclusion from the requirement to prepare an environment assessment statement per 21 CFR 25.31(a). Certification of compliance with all federal, state, and local environmental laws is included.

cc: ANDA 90-379
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 11/9/10
HFD-640/RRajagopalan/11/12/10
HFD-617/FNice/11/12/10

F/T by:

V:\Firmsam\barr\Ltrs&Rev\90-379c4

APPROVABLE

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

/s/

KAREN A BERNARD
11/12/2010

RADHIKA RAJAGOPALAN
11/12/2010

FRANK J NICE
11/15/2010

ANDA 90379

Budesonide Enteric Coated Capsules

Teva Pharmaceuticals USA Inc.

Karen A. Bernard, Ph.D.

Office of Generic Drugs
Division of Chemistry II

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 3
The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

Chemistry Review Data Sheet

1. ANDA 90-379

2. REVIEW #: 3

3. REVIEW DATE: July 13, 2010

4. REVIEWER: Karen Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2008
Amendment	April 1, 2009
Amendment	September 22, 2009
Amendment	November 2, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	April 23, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA Inc

Address: 400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Representative: Nicholas Tantillo

Telephone: 201-930-3650

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Budesonide Enteric Coated Capsules

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject ANDA is the reference listed drug, Entocort® EC (NDA 21-324), manufactured by Astra Zeneca.

10. PHARMACOL. CATEGORY: Budesonide is indicated for the treatment of the signs and symptoms of Crohns Disease.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature: 16α,17-[(1RS)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (Technical Package)
(RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (Technical Package, USP)
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(R)] (USP)

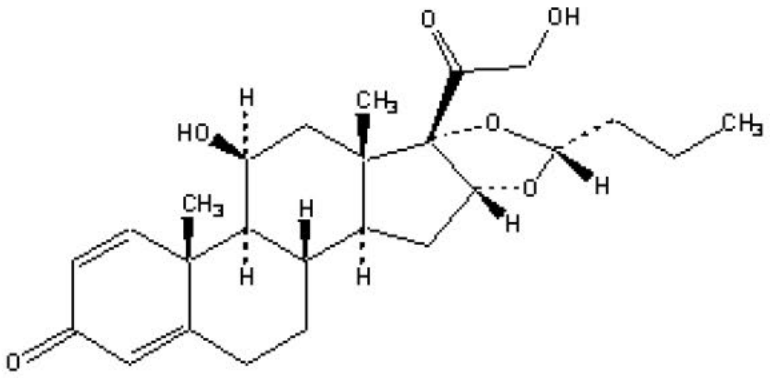
16α,17-[(S)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (USP)

CAS #: [51372-29-3; 51372-28-2; 51333-22-3]

USAN: Budesonide

Molecular Structure:

Mixture of epimer A and epimer B



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	inadequate	7/13/10	Review by K. Bernard

**Other DMFs for (b) (4) are cited but enough information was provided in ANDA so they were not reviewed or used in the review.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not Applicable		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	6/16/08	
Methods Validation	Not Applicable		
Labeling	Acceptable	5/15/09	A. Payne
Bioequivalence	Acceptable	3/5/09	O. Anand
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-379

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective the application is not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Budesonide is a white to off-white (b) (4) powder. It is practically insoluble in water and heptane and freely soluble in chloroform. (b) (4) (b) (4). It is a mixture of 2 epimers A and B. It is the subject of USP and EP monographs The drug product is an orally administered capsule with a maximum daily dosage of 9 mg (3 x 3mg). It is supplied in HDPE bottles of (b) (4) 100 .

1) Description of How the Drug Product is Intended to be Used

Budesonide Capsules are used for Crohns Disease. The maximum daily dosage for Budesonide is 9 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval.

Following this page, 63 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

R REGIONAL INFORMATION

R.3.S Method Validation Package – Provided in appropriate section.

R.1.P.1 Executed Batch Records – Provided in appropriate section.

R.1.P.2 Information on Components – Provided in appropriate section.

R.2.P Comparability Protocols - Not applicable.

R.3.P Methods Validation Package – Provided in appropriate section.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert - From chemistry's perspective information in the description and how supplied sections of the package insert corresponds with information provided in the application.

B. Environmental Assessment Or Claim Of Categorical Exclusion - The applicant requests a categorical exclusion from the requirement to prepare an environment assessment statement per 21 CFR 25.31(a). Certification of compliance with all federal, state, and local environmental laws is included.

III. List Of Deficiencies To Be Communicated

ANDA: 90-379
APPLICANT: Teva Pharamceuticals, Inc.
DRUG PRODUCT: Budesonide Enteric-Coated Capsules (Delayed Release), 3 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

3.

4.

(b) (4)

5.

6.

7.

8. For ease of review, it is also recommended that you submit a copy of your amendment response in MS Word.

Sincerely yours,

{See appended electronic signature}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-379
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 7/13/10
HFD-640/RRajagopalan/8/3/10
HFD-617/FNice8/6/10

F/T by:

V:\Firmsam\barr\Ltrs&Rev\90-379c3

NOT APPROVABLE- MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90379	ORIG-1	BARR LABORATORIES INC	BUDESONIDE

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

/s/

KAREN A BERNARD
08/06/2010

FRANK J NICE
08/06/2010

RADHIKA RAJAGOPALAN
08/09/2010

ANDA 90-379

Budesonide Enteric Coated Capsules

Teva Pharmaceuticals USA Inc.

Karen A. Bernard, Ph.D.

Office of Generic Drugs
Division of Chemistry II

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 3
The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 8

C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

Chemistry Review Data Sheet

1. ANDA 90-379

2. REVIEW #: 2

3. REVIEW DATES: September 10, 2009, October 1, 2009, November 9, 2009 and November 18, 2009

4. REVIEWER: Karen Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	January 31, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	April 1, 2009
Amendment	September 22, 2009
Amendment	November 2, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Barr Laboratories Inc.
(subsidiary of Teva Pharmaceuticals USA Inc)

Address: 400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Representative: Tracey Mathew

Telephone: 201-930-3609

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Budesonide Enteric Coated Capsules

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject ANDA is the reference listed drug, Entocort® EC (NDA 21-324), manufactured by Astra Zeneca.

10. PHARMACOL. CATEGORY: Budesonide is indicated for the treatment of the signs and symptoms of Crohns Disease.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature: 16α,17-[(1RS)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (Technical Package)
(RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (Technical Package, USP)

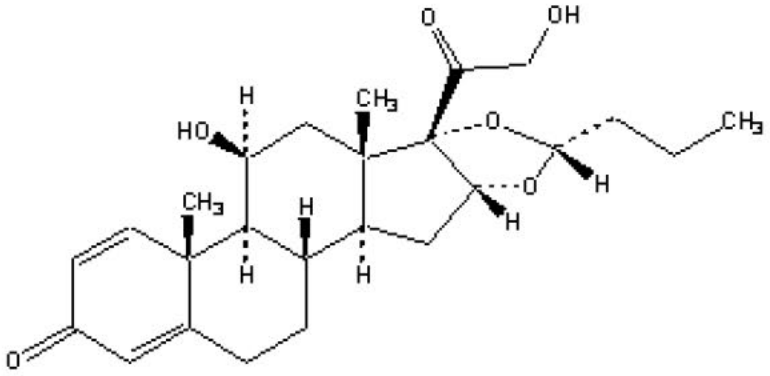
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(R)] (USP)
16α,17-[(S)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (USP)

CAS #: [51372-29-3; 51372-28-2; 51333-22-3]

USAN: Budesonide

Molecular Structure:

Mixture of epimer A and epimer B



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	9/11/09	Review by ESchaeffer

**Other DMFs for (b) (4) are cited but enough information was provided in ANDA so they were not reviewed or used in the review.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not Applicable		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	6/16/08	
Methods Validation	Not Applicable		
Labeling	Acceptable	5/15/09	A. Payne
Bioequivalence	Acceptable	3/5/09	O. Anand
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-379

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective the application still contains some issues and is not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Budesonide is a white to off-white (b) (4) powder. It is practically insoluble in water and heptane and freely soluble in chloroform. (b) (4) (b) (4). It is a mixture of 2 epimers A and B. It is the subject of USP and EP monographs The drug product is an orally administered capsule with a maximum daily dosage of 9 mg (3 x 3mg). It is supplied in HDPE bottles of (b) (4) 100 .

1) Description of How the Drug Product is Intended to be Used

Budesonide Capsules are used for Crohns Disease. The maximum daily dosage for Budesonide is 9 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval..

Following this page, 57 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

R REGIONAL INFORMATION

R.3.S Method Validation Package – Provided in appropriate section.

R.1.P.1 Executed Batch Records – Provided in appropriate section.

R.1.P.2 Information on Components – Provided in appropriate section.

R.2.P Comparability Protocols - Not applicable.

R.3.P Methods Validation Package – Provided in appropriate section.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert - From chemistry's perspective information in the description and how supplied sections of the package insert corresponds with information provided in the application.

B. Environmental Assessment Or Claim Of Categorical Exclusion - The applicant requests a categorical exclusion from the requirement to prepare an environment assessment statement per 21 CFR 25.31(a). Certification of compliance with all federal, state, and local environmental laws is included.

III. List Of Deficiencies To Be Communicated

ANDA: 90-379
APPLICANT: Barr Laboratories, Inc.
DRUG PRODUCT: Budesonide Enteric-Coated Capsules (Delayed Release), 3 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

(b) (4)

3.

4.

5.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-379
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 11/18/09
HFD-640/DMaldonado/12/7/09
HFD-617/TLiu/12/7/09

F/T by:

V:\Firmsam\barr\Ltrs&Rev\90-379c2

NOT APPROVABLE- MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90379	ORIG-1	BARR LABORATORIES INC	BUDESONIDE

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

/s/

KAREN A BERNARD
12/07/2009

THERESA C LIU
12/07/2009

DAMARIS C MALDONADO
12/07/2009

ANDA 90-379

Budesonide Enteric Coated Capsules

Barr Laboratories Inc.

Karen A. Bernard, Ph.D.

Office of Generic Drugs
Division of Chemistry II

Table of Contents

Table of Contents 2
Chemistry Review Data Sheet 3
The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 7

C. Basis for Approvability or Not-Approval Recommendation 7

Chemistry Assessment 8

Chemistry Review Data Sheet

1. ANDA 90-379

2. REVIEW #: 1

3. REVIEW DATE: August 4, 2008

4. REVIEWER: Karen Bernard, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not Applicable	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	January 31, 2008

7. NAME & ADDRESS OF APPLICANT:

Name: Barr Laboratories Inc.

Address: 223 Quaker Road
PO Box 2900
Pomona, NY 10970-0519

Representative: Nicholas Tantillo

Telephone: 201-930-3650

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not Applicable
b) Non-Proprietary Name (USAN): Budesonide Enteric Coated Capsules

9. LEGAL BASIS FOR SUBMISSION: The basis of the subject ANDA is the reference listed drug, Entocort® EC (NDA 21-324), manufactured by Astra Zeneca.

10. PHARMACOL. CATEGORY: Budesonide is indicated for the treatment of the signs and symptoms of Crohns Disease.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 3 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Nomenclature: 16α,17-[(1RS)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (Technical Package)
(RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde (Technical Package, USP)
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(R)] (USP)

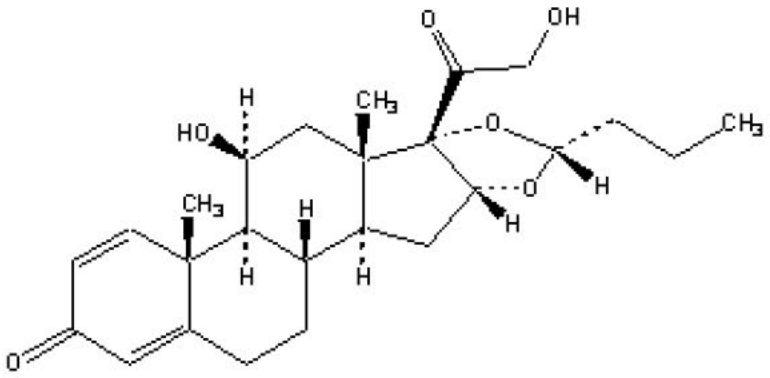
16α,17-[(S)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione (USP)

CAS #: [51372-29-3; 51372-28-2; 51333-22-3]

USAN: Budesonide

Molecular Structure:

Mixture of epimer A and epimer B



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.53

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	6/08	Review by KFurnkranz

**Other DMFs for (b) (4) are cited but enough information was provided in ANDA so they were not reviewed or used in the review.

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Not Applicable		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Not Applicable		
EES	Acceptable	6/16/08	
Methods Validation	Not Applicable		
Labeling	Pending		
Bioequivalence	Deficient	7/29/08	
EA	Not Applicable (category exclusion)		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-379

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective the application is not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance Budesonide is a white to off-white (b) (4) powder. It is practically insoluble in water and heptane and freely soluble in chloroform. (b) (4) (b) (4). It is a mixture of 2 epimers A and B. It is the subject of USP and EP monographs The drug product is an orally administered capsule with a maximum daily dosage of 9 mg (3 x 3mg). It is supplied in HDPE bottles of (b) (4) 100 .

1) Description of How the Drug Product is Intended to be Used

Budesonide Capsules are used for Crohns Disease. The maximum daily dosage for Ropinirole is 9 mg.

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval (b) (4)

Following this page, 33 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

R REGIONAL INFORMATION

R.3.S Method Validation Package – Provided in appropriate section.

R.1.P.1 Executed Batch Records – Provided in appropriate section.

R.1.P.2 Information on Components – Provided in appropriate section.

R.2.P Comparability Protocols - Not applicable.

R.3.P Methods Validation Package – Provided in appropriate section.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert - From chemistry's perspective information in the description and how supplied sections of the package insert corresponds with information provided in the application.

B. Environmental Assessment Or Claim Of Categorical Exclusion - The applicant requests a categorical exclusion from the requirement to prepare an environment assessment statement per 21 CFR 25.31(a). Certification of compliance with all federal, state, and local environmental laws is included.

III. List Of Deficiencies To Be Communicated

ANDA: 90-379
APPLICANT: Barr Laboratories, Inc.
DRUG PRODUCT: Budesonide Enteric-Coated Capsules (Delayed Release), 3 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

3.

4.

5.

6.

Following this page, 2 Pages Withheld in Full as (b)(4)

23. (b) (4)

24.

25. The label storage conditions should read: "Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Sincerely yours,

{electronic signature on file}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-379
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/KBernard 8/4/08
HFD-640/DMaldonado/ 8/21/08
HFD-617/TLiu/8/22/08

F/T by:

V:\Firmsam\barr\Ltrs&Rev\90-379c1

TYPE OF LETTER: NOT APPROVABLE

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

/s/

Karen A. Bernard
8/22/2008 04:01:01 PM
CHEMIST

Theresa Liu
8/25/2008 09:42:22 AM
CSO

Damaris Maldonado
8/25/2008 10:01:37 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090379	
Drug Product Name	Budesonide Capsules	
Strength(s)	3 mg	
Applicant Name	Barr Laboratories, Inc.	
Applicant Address	223 Quaker Road, P.O.Box 2900, Pomona, NY 10970.	
US Agent Name and the mailing address	Nicholas Tantillo, Sr. Director, Regulatory Affairs	
US agent's Telephone Number	(201) 930-3650	
US Agent's Fax Number	(201)-930-3318	
Original Submission Date(s)	01/31/2008	
Submission Date(s) of Amendment(s) Under Review	07/26/2011 (Telephone Amendment)	
First Generic (Yes or No)	No	
Reviewer	Haritha Mandula, Ph.D.	
Study Number (s)	10716217	10716218
Study Type (s)	Fasting	Fed
Strength (s)	3 mg	3 mg
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	3320 Walnut Bend Lane Houston, Texas 77042-4712	
Analytical Site	(b) (4)	
Analytical Site Address		

DSI Status	**ADEQUATE**		
REVIEW RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Fasting Study**	**3 mg**	**ADEQUATE**
1	**Fed Study**	**3 mg**	**ADEQUATE**
1	**Dissolution**	**3 mg**	**ADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Barr Laboratories Inc.'s Budesonide Capsule, 3 mg, to the corresponding reference product, Astrazeneca's Entocort EC® (Budesonide) capsule, 3 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The firm's fasting and fed BE studies are incomplete due to bioanalytical deficiencies. The results are summarized in the tables below.

Budesonide, 3 x 3 mg Fasting Bioequivalence Study No. 10716217, N=79 (Male=43 and Female=36) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	10916.83	9851.42	1.11	105.60	116.28
AUC∞ (pg·hr/mL)	11253.65	10304.85	1.09	104.29	114.35
Cmax (pg/mL)	1115.29	1006.96	1.11	103.60	118.42

Budesonide, 3 x 3 mg Fed Bioequivalence Study No. 10716218, N=23 (Male=17 and Female=6) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	14179.51	14702.81	0.96	91.04	102.16
AUC∞ (pg·hr/mL)	14467.95	15045.22	0.96	91.04	101.58
Cmax (pg/mL)	2039.61	2133.08	0.96	86.39	105.83

There is no USP or FDA-recommended dissolution testing method for this test product. The firm has conducted acceptable comparative dissolution testing on all strengths using its own method which was found acceptable by the FDA (DARRTS Search; ANDA 090379; REV-BIOEQ-02 (Dissolution Review): Final Date: 07/25/2008). On 02/09/2009, the firm has acknowledged the FDA-recommended dissolution specification. The firm's dissolution test is complete.

No Division of Scientific Investigations (DSI) inspection is pending or necessary. The clinical site was last inspected on 2/15/2010 for NDA 22-439 and the outcome was NAI. The analytical site was last inspected on (b) (4) for NDA (b) (4) and the outcome was (b) (4). The reviewer also evaluated the inspectional findings from NDA (b) (4) (b) (4) and 21-875 (b) (4) and their impact on the outcome of the current ANDA. The findings from these NDAs do not seem to have any impact on the outcome of the current ANDA.

In the original submission, the firm did not submit the required 20% chromatograms and the raw chromatographic data for all the subjects for the fasting and fed BE studies. On

07/25/2011[1], a telephone request was placed to the firm. On 07/26/2010[2], the firm provided the required information.

The application is acceptable with no deficiencies.

APPEARS THIS WAY ON ORIGINAL

[1] Darrts Search: ANDA 090379; COR-ANDAIR-01 (Advice/Information Request); Final Date: 07/25/2011.
[2] Electronic Document Room: ANDA 090379; Bioequivalence/Response to Information Request; Final Date: 07/26/2011.

2 TABLE OF CONTENTS

1 Executive Summary 2
2 Table of Contents 4
3 Submission Summary 5
3.1 Drug Product Information 5
3.2 PK/PD Information 5
3.3 OGD Recommendations for Drug Product 5
3.4 Contents of Submission 7
3.5 Pre-Study Bioanalytical Method Validation 8
3.6 In Vivo Studies 10
3.7 Formulation 16
3.8 In Vitro Dissolution 16
3.9 Deficiency Comments 17
3.10 Recommendations 17
3.11 Comments for Other OGD Disciplines 19
4 Appendix 20
4.1 Individual Study Reviews 20
4.1.1 Single-dose Fasting Bioequivalence Study 20
4.1.1.1 Study Design 20
4.1.1.2 Clinical Results 23
4.1.1.3 Bioanalytical Results 26
4.1.1.4 Pharmacokinetic Results 28
4.1.2 Single-dose Fed Bioequivalence Study 33
4.1.2.1 Study Design 33
4.1.2.2 Clinical Results 37
4.1.2.3 Bioanalytical Results 40
4.1.2.4 Pharmacokinetic Results 42
4.2 Formulation Data 48
4.3 Dissolution Data 52
4.4 Division of Scientific Investigation (DSI) Inspection Report Review 56
4.4.1 Summarization of the DSI Inspection of Clinical Site 56
4.4.2 Summarization of the DSI Inspection of Analytical Site 56
4.5 Detailed Regulatory History (If Applicable) 61
4.6 Consult Reviews 62
4.7 SAS Output 63
4.7.1 Fasting Study Data 63
4.7.2 Fasting Study Output 74
4.7.3 Fed Study Data 86
4.7.4 Fed Study Output 89
4.8 Additional Attachments 98
4.9 Outcome Page 101

3 SUBMISSION SUMMARY

3.1 Drug Product Information[3, 4]

Test Product	Budesonide Capsules, 3 mg
Reference Product	ENTOCORT EC® (Budesonide) Capsules, 3 mg
RLD Manufacturer	AstraZeneca
NDA No.	021324
RLD Approval Date	October 2, 2001
Indication	• For the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. • For the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.

3.2 PK/PD Information[4, 5, 6]

Bioavailability	The absorption of ENTOCORT EC® seems to be complete, although Cmax and Tmax are variable. The systemic availability after a single dose is higher in patients with Crohn's disease compared to healthy volunteers (21% vs 9%) but approaches that in healthy volunteers after repeated dosing.
Food Effect	A mean delay in time to peak concentration of 2.5 hours is observed with the intake of high-fat meal with no significant differences in AUC
Tmax	Time to peak concentration varies in individual patients between 30 and 600 minutes.
Metabolism	Budesonide undergoes approximately 85% first pass metabolism to two inactive metabolites: 16alpha-hdroxyprednisolone (24%) and 6beta-hydroxybudesonide (5%).
Excretion	Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [3H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.
Half-life	The plasma elimination half-life, $t_{1/2}$, after administration of intravenous doses ranges between 2.0 and 3.6 hours, and does not differ between healthy adults and patients with Crohn's disease.
Dosage and Administration	The recommended adult dosage for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon is 9 mg taken once daily in the morning for up to 8 weeks. Repeated 8

[3] Online-Orange Book. http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
[4] Labeling for the RLD Product:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021324s008lbl.pdf
[5] Online-Clinical Pharmacology. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=585
[6] http://www.rxlist.com/script/main/hp.asp

	week courses of Entocort EC can be given for recurring episodes of active disease. Following an 8 week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI < 150), Entocort EC 6 mg is recommended once daily for maintenance of clinical remission up to 3 months. If symptom control is still maintained at 3 months an attempt to taper to complete cessation is recommended. Continued treatment with Entocort EC 6 mg for more than 3 months has been shown to provide substantial clinical benefit. Entocort EC capsules should be swallowed whole and not chewed or broken.
Maximum Daily Dose	9 mg taken once daily
Drug Specific Issues (if any)	Pregnancy Category C: Budesonide was teratogenic and embryocidal in rabbits and rats. There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Glucocorticosteroids are secreted in human milk. The amount of budesonide secreted in breast milk has not been determined. Caution should be taken in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover *in vivo*
	Strength:	3 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	3 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Budesonide in plasma
Bioequivalence based on:	90% CI of Budesonide
Waiver request of in-vivo testing:	N/A

Source of most recent recommendations:	Guidance for Industry: Individual Product Bioequivalence Recommendations: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188518.pdf; Draft Guidance: 10/2009.
Summary of OGD or DBE History (for details, see Appendix 4.5):	There is one approved ANDA for Budesonide Capsules in Orange Book ANDA 90410: Budesonide Capsule, 3 mg; Mylan; Approval date: May 16, 2011.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Pre-Study Bioanalytical Method Validation

Bioanalytical Method Validation Report Location	5.3.1.4 Fasting Study
Analyte	Budesonide
Internal Standard (IS)	(b) (4)
Method Description	Liquid-liquid
Limit of Quantitation (pg/mL)	10.0
Average Recovery of Drug (%)	84.5%
Average Recovery of IS (%)	85.1%
Standard Curve Concentrations (pg/mL)	10.0, 20.0, 50.0, 100, 250, 500, 1250, 2500
QC Concentrations (pg/mL)	10.0, 30.0, 150, 2000
QC Intraday Precision Range (%)	1.89 to 11.5%
QC Intraday Accuracy Range (%)	-5.29 to 6.08%
QC Interday Precision Range (%)	3.17 to 10.3%
QC Interday Accuracy Range (%)	-1.72 to -0.232%
Bench-top Stability (hrs)	25.5 hours at room temperature
Stock Stability (days)	406 days at -20°C; IS 417 days at -20°C
Processed Stability (hrs)	76.75 hours at room temperature
Freeze-Thaw Stability (Cycles)	4 cycles
Long-Term Storage Stability (days)	525 days at -20°C
Dilution Integrity	150 pg/mL diluted 2-fold; 5000 pg/mL diluted 5-fold
Selectivity	No interfering peaks noted in the blank plasma samples.

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes, the firm chose three Calibration Standard (20.0 pg/ml, 100 pg/ml and 1250 pg/ml) to conduct the recovery study. The mean recoveries of these Standards are 83.5%, 81.5% and 88.5%.
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	Not applicable
Was the dilution factor adequate for the current study sample analysis?	Yes
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	Yes
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Comments on the Pre-Study Method Validation:

1. Method Description: [redacted] (b) (4)

2. Human plasma containing tripotassium EDTA (K3 EDTA) as the anticoagulant was supplied by [redacted] (b) (4) and biochemed was pooled and used in preparation of quality controls and calibration standards as well as for blanks containing matrix. The same anticoagulant (K3 EDTA) was used during the actual sample analysis.

3. For the fasting study, the firm reanalyzed 1% of the samples for above upper limit of quantitation. For the fed study, the firm reanalyzed 5% of the samples for above upper limit of quantitation. For analytical runs which contained diluted subject samples, the appropriate level quality control pool was diluted and analyzed in a similar manner to validate the dilution of study samples.

4. The CV% associated with recovery of the drug was 9.9% and that associated with internal standard was 9.2%.

5. The pre-study method validation is acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No. 10716217	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters ± SD (%CV)[1]						Study Report Location
					Cmax (ng/ml)	Tmax (hr)	AUC0-t (pg-h/ml)	AUC∞ (pg-h/ml)	T½ (hr)	Ke (1/hr)	
Study No. 10716217	Study title: A Relative Bioavailability Study of Two Budesonide 3 mg Controlled Release Capsule Formulations Under Fasting Conditions	Randomized, Single-Dose, Two-way, Cross-over	**Test Product A** Budesonide 3 mg capsules Barr Laboratories, Inc. Batch No: 800206 Mfd. Date: 09/07/2007	79 completing (43 M/36 F) Healthy subjects mean age: 32.09 (18– 63)	1291.0380 ± 796.1365 (61.6664)	4.7538 ± 1.8804 (39.5566)	12624.2914 ± 7087.7233 (56.1435)	12966.4177 ± 7269.9130 (56.0672)	5.5944 ± 1.0400 (18.5899)	0.1277 ± 0.0214 (16.7886)	Module 2
			Ref Product B ENTOCORT EC® (budesonide) 3 mg capsules AstraZeneca AB Lot No: NC0077 Exp. Date: 11/30/2009		1181.4937 ± 665.8180 (56.3539)	4.9055 ± 1.7881 (36.4502)	11399.1667 ± 6512.5718 (57.1320)	11827.5793 ± 6663.6568 (56.3400)	6.1224 ± 1.4829 (24.2216)	0.1187 ± 0.0245 (20.6425)	

Reviewer's note: There is an error in the table for the units of Cmax. It should be pg/mL instead of ng/mL.

Study Ref. No. 10716218	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters ± SD (%CV)[1]						Study Rep-ort Loca-tion
					Cmax (ng/ml)	Tmax (hr)	AUC0-t (pg-h/ml)	AUC∞ (pg-h/ml)	T½ (hr)	Ke (1/hr)	
Study No. 10716218	Study title: A Relative Bioavailability Study of Two Budesonide 3 mg Controlled Release Capsule Formulations Under Non-Fasting Conditions	Randomized, Single-Dose, Two-way, Cross-over	**Test Product A** Budesonide 3 mg capsules Barr Laboratories, Inc. Batch No: 800206 Mfr. Date: 09/07/2007	23 completing (17 M/ 6 F) Healthy subjects mean age: 31.3 (21– 56)	2387.3913 ± 1593.8581 (66.7615)	6.2609 ± 1.9180 (30.6353)	15888.4855 ± 9179.5566 (57.7749)	16140.7852 ± 9221.8350 (57.1337)	5.1554 ± 0.8112 (15.7340)	0.1374 ± 0.0203 (14.7784)	Module 2
			Ref Product B ENTOCORT EC® (budesonide) 3 mg capsules AstraZeneca AB Lot No: NC0077 Exp. Date: 11/30/2009		2549.1739 ± 1783.5981 (69.9677)	6.4348 ± 1.9674 (30.5740)	17220.1982 ± 11504.1714 (66.8063)	17503.9406 ± 11565.1279 (66.0716)	5.0111 ± 0.7737 (15.4400)	0.1414 ± 0.0213 (15.0436)	

Note: There is an error in the table for the units of Cmax. It should be pg/mL instead of ng/mL.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Budesonide controlled release capsule 3 x 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. 10716217					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	10916.83	9851.42	1.11	105.60	116.28
AUC∞ (hr *pg/ml)	11253.65	10304.85	1.09	104.29	114.35
Cmax (pg/ml)	1115.29	1006.96	1.11	103.60	118.42

Budesonide controlled release capsule 3 x 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. 10716218					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	14179.51	14702.81	0.96	91.04	102.16
AUC∞ (hr *pg/ml)	14467.95	15045.22	0.96	91.04	101.58
Cmax (pg/ml)	2039.61	2133.08	0.96	86.39	105.83

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE? Yes

Table 3. Reanalysis of Study Samples

Bioequivalence Study 10716217				
Reason for Reanalysis	**Number of Samples Reanalyzed**		**Number of Recalculated Values Used After Reanalysis[4]**	
	Actual Number (% of Total Samples)		**Actual Number (% of Total Samples)**	
	Test N=1500[2]	**Reference N=1500[2]**	**Test N=1500[2]**	**Reference N=1500[2]**
	n (%)[3]	**n (%)[3]**	**n (%)[3]**	**n (%)[3]**
Pharmacokinetic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Analytical - Extraction Error	0 (0.00%)	1 (0.07%)	0 (0.00%)	0 (0.00%)[5]
- Unacceptable internal standard	0 (0.00%)	1 (0.07%)	0 (0.00%)	0 (0.00%)[5]
- Result above upper limit of quantitation	20 (1.33%)	12 (0.80%)	0 (0.00%)[5]	0 (0.00%)[5]
Total	20 (1.33%)	14 (0.93%)	0 (0.00%)[5]	0 (0.00%)[5]

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table

[2] N = Number of samples analyzed for each treatment

[3] n = Number of samples repeated; (%) = percentage of assays repeated (i.e. 100*(n/N)%)

[4] Reported values that are different from the original value

[5] Reviewer's notes: The firm refers to this table foot note 4 for reported values that are different from the original value. Since the original values were NR in all the repeated cases, the firm therefore denotes "0%" in these columns.

Bioequivalence Study 10716218				
Reason for Reanalysis	**Number of Samples Reanalyzed**		**Number of Recalculated Values Used After Reanalysis[4]**	
	Actual Number (% of Total Samples)		**Actual Number (% of Total Samples)**	
	Test N=437[2]	**Reference N=437[2]**	**Test N=437[2]**	**Reference N=437[2]**
	n (%)[3]	**n (%)[3]**	**n (%)[3]**	**n (%)[3]**
Pharmacokinetic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Analytical -Unacceptable internal standard response	5 (1.14%)	5 (1.14%)	0 (0.00%)[5]	0 (0.00%)[5]
-Result above upper limit of quantitation	18 (4.12%)	25 (5.72%)	0 (0.00%)[5]	0 (0.00%)[5]
Total	23 (5.26%)	30 (6.86%)	0 (0.00%)[5]	0 (0.00%)[5]

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table

[2] N = Number of samples analyzed for each treatment

[3] n = Number of samples repeated; (%) = percentage of assays repeated (i.e. 100*(n/N)%)

[4] Reported values that are different from the original value

[5] Reviewer's notes: The firm refers to this table foot note 4 for reported values that are different from the original value. Since the original values were NR in all the repeated cases, the firm therefore denotes "0%" in these columns.

Please provide detailed explanation for all repeats not related to analytical reasons.

All the repeats were related to analytical reasons.

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Conduct of an Analytical Study

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria: **analytical and pharmacokinetic**	Yes. There were no pharmacokinetic repeats
If not, list the criteria that you don't agree and provide additional comment below	
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	
Did reviewer reanalyze study results?	Yes
Was the study outcome changed based on reviewer reanalysis?	No
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DBE?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Comments from the Reviewer:

1. For the fasting study (Study No. 10716217), the samples were reanalyzed due to analytical extraction error (1 sample from reference treatment), Unacceptable internal standard (1 sample from reference treatment) and due to result above upper limit of quantitation (20 samples from test treatment and 12 samples from reference treatment).

2. For the fed study (Study No. 10716218), the samples were reanalyzed due to analytical extraction error (5 samples from the test treatment and 5 samples from the reference treatment), and due to result above upper limit of quantitation (18 samples from test treatment and 25 samples from reference treatment).

3. In the original submission, the firm did not submit the required 20% chromatograms and the raw chromatographic data for all the subjects for the fasting and fed BE studies. On 07/25/2011[1], a telephone request was placed to the firm. On 07/26/2010[2], the firm provided the required information.

4. In both studies, all of the samples were reanalyzed in accordance with the firm's standard operating procedure (SOP), Conduct of an Analytical Study, Procedure No. (b) (4), Effective Date: (b) (4)

5. The repeat values for the dilute samples as compared with the highest standard concentration were equal to or greater than the highest standard concentration. None of the repeated values for the dilute samples were lower than 15% from the highest standard concentration. The firm's repeat analysis is acceptable.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	Not applicable, the formulation is a capsule
If a tablet, is the test product biobatch scored	Not applicable, the formulation is a capsule
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS[7]
Submitted Method (USP, FDA, or Firm)	Firm's own method
Recommended Method (details below)	There is no USP or FDA-recommended method. The firm's proposed dissolution method was found to be acceptable. Please note currently this method is listed in the External Dissolution Database as the FDA-recommended method for this drug product
Medium	First 2 hours: Acid Stage, 0.1 N HCl 1-6 hours: Buffer Stage, Phosphate Buffer, pH 7.5.
Volume (mL)	Acid Stage: 1000 mL Buffer Stage: 1000 mL
USP Apparatus type	USP Apparatus 2 (Paddle), with capsule sinker
Rotation (rpm)	75 rpm
Specifications	Acid Stage: 2 hrs: NMT (b)(4)% of Budesonide Dissolved Buffer Stage: 1 hr: (b)(4)% 2 hr: % 4 hr: % 6 hr: NLT (b)(4)%
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	Yes. The firm's test product passes the acid stage specification at the A1 level and the buffer stage specification at the L1 level.
If a modified-release tablet, was testing done on ½ tablets?	Not applicable
F2 metric calculated?	F2 value for test vs reference product is 43.85.
If no, reason why F2 not calculated	
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

Reviewer's Comments:

1. There is no USP or FDA-recommended dissolution testing method for this test product.

[7] DARRTS Search; ANDA 090379; REV-BIOEQ-02 (Dissolution Review): Final Date: 07/25/2008.

2. The firm conducted dissolution testing with its own proposed method. Please note currently this method is listed in the External Dissolution Database as the FDA-recommended method for this drug product.
3. The RLD used a two stage dissolution method using USP apparatus 4 with flow-through cells. The RLD also conducted dissolution testing on one composite sample consisting of the contents from 8 capsules. The firm is using individual units for conducting the dissolution testing.
4. The firm's proposed dissolution method was found acceptable. However, the Division of Bioequivalence (DBE) deemed the firm's proposed dissolution specifications for the buffer stage as (b) (4) and based on the firm's submitted dissolution data, recommended the following specifications for the buffer stage: 1 hr: (b) (4)%; 2 hrs: (b) (4)%; 4 hrs: (b) (4)%; and 6 hrs: NLT (b) (4)%. The firm's test product passes the acid stage specification at the A1 level and the buffer stage specifications at the L1 level[8]. The firm should indicate if it accepts the DBE-recommended specifications. On 07/29/2008[9], a deficiency letter was sent to the firm. On 02/09/2009, the firm sent its response to the deficiency letter. The firm had satisfactorily responded to all deficiencies. The firm had also acknowledged the DBE-recommended specifications[10].
5. The firm also conducted and submitted comparative dissolution testing in three additional media: (pH 1.2, pH 4.5 and pH 6.8). There is no evidence of dose-dumping of the test product.

3.9 Deficiency Comments

None

3.10 Recommendations

[8] (b) (4)

[9] DARRTS Search; ANDA 090379; COR-ANDADE-01 (Bio Incomplete Deficiencies); Final Date: 07/29/2008.

[10] DARRTS Search: ANDA 090379; REV-BIOEQ-01 (General Review); Final Date: 03/05/2009.

1. The Division of Bioequivalence finds the fasting BE study (10716217) conducted by Barr Laboratories, Inc. on its Budesonide Capsules, 3 mg (lot # 800206) comparing it to Astrazeneca's Entocort EC® (Budesonide) Capsules, 3 mg Base (lot # NC0077), acceptable.

2. The Division of Bioequivalence finds the fed BE study (10716218) conducted by Barr Laboratories, Inc. on its Budesonide Capsules, 3 mg (lot # 800206) comparing it to Astrazeneca's Entocort EC® (Budesonide) Capsules, 3 mg Base (lot # NC0077), acceptable.

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted using the following method and specification.

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37ºC		**Volume**
First 2 hours;	Acid stage	0.1 N HCl or 0.01 N HCl, pending clarification	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4 and 6 hours		

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

The firm should be informed of the above recommendations

3.11 Comments for Other OGD Disciplines

Discipline	Comment

APPEARS THIS WAY ON ORIGINAL

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	10716217
Study Title	A Relative Bioavailability Study of Two Budesonide 3 mg Controlled Release Capsule Formations Under Fasting Conditions
Clinical Site (Name & Address)	Novum Pharmaceutical Research Services 3320 Walnut Bend Lane Houston, Texas 77042-4712 832-251-8100
Principal Investigator	Soran Hong, M.D.
Dosing Dates	Period I: 10/07/07 Period II: 10/14/07
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	11/12/2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Long Term Freezer stability has been established at 525 days @ -20°C 27 Days Sample collection started on 10/7/07 and was completed on 11/2/07.

Table 6. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Budesonide Enteric Coated Capsule	Entocort® EC
Manufacturer	Barr Laboratories, Inc.	AstraZeneca
Batch/Lot No.	800206	NC0077
Manufacture Date	3/15/2007	N/A
Expiration Date	N/A	11/30/09
Strength	3mg	3mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4) capsules	N/A

Production Batch Size	(b) (4) capsules	N/A
Potency (Assay)	3mg	3mg
Content Uniformity (expressed as mean, %CV or per USP)	102.7, 0.1%	102.6, 0.4%
Dose Administered	3mg	3mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	Yes, Entocort EC capsules should be swallowed whole and not chewed or broken.
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	Yes, (b) (4) capsules.

Table 7. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	**Enrolled: 80** **Dosed: 80** **Completed: 79**[11] **Samples Analyzed: 79** **Data Analyzed: 79**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	AB: 02, 04, 05, 08, 10, 12, 13, 15, 18, 19, 22, 24, 25, 28, 29, 31, 34, 36, 38, 39, 42, 43, 45, 48, 50, 52, 53, 56, 58, 60, 62, 64, 66, 68, 69, 71, 74, 76, 77 and 79. BA: 01, 03, 06, 07, 09, 11, 14, 16, 17, 20, 21, 23, 26, 27, 30, 32, 33, 35, 37, 40, 41, 44, 46, 47, 49, 51, 54, 55, 57, 59, 61, 63, 65, 67, 70, 72, 73, 75, 78 and 80.
Blood Sampling Times	Pre-dose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 15, 18, 24, and 36 hours.
Blood Volume Collected/Sample	The total volume of blood collected over the duration of the sudy for pharmacokinetic sampling and safety testing for each subject was approximately 316 mL over an approximate 5 week period (including the 28-day screening window).
Anticoagulant Used	K3 EDTA.

[11] Subject 36 did not return for Period II check-in on 10/12/07 for personal reasons. This subject did complete end-of-study evaluations with good results.

Blood Sample Processing & Storage (include storage temperature)	In each period, 7 mL venous blood was collected in K3 EDTA Vacutainers prior to dosing and at the times as mentioned in blood sampling times. The samples were labeled at the time of collection with a unique code number, and within 60 minutes of collection, were centrifuged at approximately 2700 rpm for 15 minutes at 4°C. The resulting plasma was separated into 2 approximately equal aliquots and placed in the freezer within 120 minutes of blood collection. Pre-dose samples were collected up to one hour before dosing. All plasma samples were stored frozen to at least -15°C. Plasma samples for all subjects completing both periods of the study were shipped to (b) (4)
IRB Approval	The protocol was reviewed and approved by the (b) (4) Independent Institutional Review Board (b) (4) on 09/11/07, prior to study commencement.
Informed Consent	The informed consent form was reviewed and approved by the (b) (4) Independent Institutional Review Board (b) (4) on 09/11/07, prior to study commencement.
Length of Fasting	The subjects received the test and reference treatments according to the randomization schedule following an overnight fast of at least 10 hours. No food or beverages (except water) were permitted during the 10-hour period leading up to dosing and during the 4 hours after dosing.
Length of Confinement	Subjects were confined at the clinical facility from at least 34 hours prior to dosing until after the 24 hour blood collection.
Safety Monitoring	The subjects were monitored throughout the study for any adverse experiences. Adverse events were collected through both solicited and unsolicited means and were subsequently coded in tabular form using the MeDRA Version 8.0 adverse event dictionary. The subjects were encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each adverse event was determined by the clinic staff based on observation and questioning of the subject. The Investigator judged the relationship of the event to the study treatments. None of the adverse events experienced by the subjects during this study were judged as serious.

Was the study design used for the fasting BE study acceptable?	YES

Comments on Study Design:

The firm used many subjects (79 completed the study) as opposed to the typical BE studies with ~24 subjects. Budesonide is not a highly variable drug as is also evident from the root mean square error associated with AUC and Cmax (for details refer to section 4.1.1.4 Pharmacokinetic results).

4.1.1.2 Clinical Results

Table 8. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 10716217			
		Treatment Groups	
		Test Product N = 79	Reference Product N = 79
Age (years)	Mean ± SD	32.09 ± 10.28	32.09 ± 10.28
	Range	18 - 63	18 - 63
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	69 (87.34%)	69 (87.34%)
	41 – 64	10 (12.65%)	10 (12.65%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	43 (54.43%)	43 (54.43%)
	Female	36 (45.57%)	36 (45.57%)
Race	Asian	1 (1.27%)	1 (1.27%)
	Biracial	1 (1.27%)	1 (1.27%)
	Black	52 (65.82%)	52 (65.82%)
	Caucasian	25 (31.64%)	25 (31.64%)
Ethnicity	Yes	15 (18.99%)	15 (18.99%)
	No	64 (81.01%)	64 (81.01%)
Weight (Lbs)	Mean ± SD	162.75 ± 30.35	162.75 ± 30.35
	Range	109 - 236	109 - 236
BMI (Kg/m^2)	Mean ± SD	25.00 ± 3.44	25.00 ± 3.44
	Range	18.3 – 30.0	18.3 – 30.0
Tobacco User	Yes	18 (22.78%)	18 (22.78%)
	No	61 (77.22%)	61 (77.22%)

Table 9. Dropout Information, Fasting Bioequivalence Study

Study 10716217				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
36	Subject 36 (b) (6) did not return for Period II check-in on 10/05/07 for personal reasons. This subject did complete end-of-study evaluations with good results.	II	No	N/A

Table 10. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Bioequivalence Study Study No. 10716217	
	Test A N (%)	Reference B N (%)
Gastrointestinal Disorders		
Diarrhoea	1 (1.25%)	0 (0%)
Nausea	0 (0%)	1 (1.27%)
Vomiting	1 (1.25%)	0 (0%)
Investigations		
Blood glucose increased	2 (2.50%)	1 (1.27%)
Blood pressure decreased	1 (1.25%)	0 (0%)
Hematology test abnormal	1 (1.25%)	0 (0%)
White blood cell count abnormal	0 (0%)	1 (1.27%)
Nervous System Disorders		
Dizziness	0 (0%)	1 (1.27%)
Headache	1 (1.25%)	3 (3.80%)
Vascular Disorders		
Epistaxis	0 (0%)	1 (1.27%)
TOTAL	**7 (8.75%)**	**8 (10.13%)**

N% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) × 100
Total N%= (Number of subjects that reported at least one AE / number of subjects dosed with respective study drug) × 100
Test product A = 80 subjects dosed, Reference product B = 79 subjects dosed.

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?
Subject 19 experienced intermittent vomiting on 10/13/2007 during period II, 29 hours prior to dosing. **The subject was allowed to continue** in the study and was dosed at 0709 on 10/14/07. Data from subjects who complete the study according to the protocol would be used in the statistical determination of bioequivalence. Per the firm's protocol, "Data from subjects experiencing emesis within 24 hours after dosing (equivalent to one dosing interval for this once-a-day product) were dropped from the study, and their samples were not sent for analysis". Subject 19 completed the study and was included in the statistical analysis.

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the

***Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?**

Yes, the vomiting occurred 29 hours prior to dosing in period II. Hence this subject was included in the analysis.

Was the adverse event profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

Yes, the adverse event profile observed during the fasting bioequivalence study was comparable for the test and reference product.

Are there any safety concerns based on the adverse event profile?
No.

Table 11. Protocol Deviations, Fasting Bioequivalence Study

Study No. 10716217		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
None		

Did dropouts/adverse events/protocol deviations affect the study outcome?
No.

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. Eighty (80) subjects were enrolled in the study, and 79 subjects completed the study. Subject 36 voluntarily withdrew from study participation.

2. Per the firm's report, "A total of 15 adverse events were reported by 15 of the 80 subjects who participated in this study. Of these events, 7 occurred after receipt of the test product, and 8 occurred after receipt of the reference product. All events associated with receipt of the test or reference capsule were considered "mild" and resolved without incident. The most common adverse events were headache and increased blood glucose. All adverse events resolved spontaneously, with the exception of 5 abnormal laboratory values". Subject 24 exhibited increased blood glucose. Subject 28 exhibited an abnormal white blood cell count. Subject 35 exhibited increased blood glucose. Subject 65 exhibited an abnormal hematology test. Subject 67 exhibited increased blood glucose."

3. None of these subjects returned to the clinical facility for repeat measurements despite repeated requests by clinic staff. These 5 subjects are considered lost to follow-up.

4. No protocol deviations were noted during this study.

4.1.1.3 Bioanalytical Results

Table 12. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 10716217 Analyte Name Budesonide								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	10.0	18.0	30.0	100	300	800	2000	2500
Inter day Precision (%CV)	7.23	4.87	4.56	4.24	4.73	3.67	4.03	3.83
Inter day Accuracy (%Actual)	97.3	99.1	100	101	102	101	99.1	100
Linearity	(Range of R2 values) 0.9978 to 0.9998							
Linearity Range (pg/mL)	10.0 to 2500							
Sensitivity/LOQ (pg/mL)	10.0							

Parameter	**Quality Control Samples**				
Concentration (pg/mL)	25.0	50.0	150	500	1880
Inter day Precision (%CV)	6.75	6.12	4.80	6.86	4.70
Inter day Accuracy (%Actual)	101	102	102	103	101
Number of Acceptable Runs	41 runs				
Number of Rejected Runs (Run ID, volume/page location)	There were no rejected runs.				
If sample and QC diluted during study, specify all dilution factors	For analytical runs which contained diluted subject samples, the appropriate level quality control pool was diluted and analyzed in a similar manner to validate the dilution of study samples. The samples were diluted 2 fold to 5-fold.				
Was 100% of raw numerical data submitted?	Yes.				

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes.
Were chromatograms serially or randomly selected?	serially
Were the chromatograms submitted by the firm acceptable?	Yes

Was the Study Assay Validation acceptable?
Acceptable.

Summary/Conclusions, Study Assays:

Per the firm, "*to demonstrate reproducible quantitation of incurred subject samples, at least 10% of the study samples were reassayed as incurred sample repeats. The repeat values were used for comparison purposes and are included in the analytical report but not used in determining the final reported value. Normal assessment of the result from the initial analysis was made and the repeat result was compared against the reportable result. Incurred sample repeats were considered acceptable if the original and reassay values from two-thirds of the repeated samples had a relative percent difference of ≤ 30%.*"

Table 13. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Conduct of an Analytical Study

Table 14. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The firm's repeat analysis is acceptable. For additional details, please refer to section 3.6: In Vivo Studies.

4.1.1.4 Pharmacokinetic Results

Table 15. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 19 and Figure 1

Fasting Bioequivalence Study, Study No. 10716217									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *pg/ml)	12620.96	56.11	2806.80	39958.25	11396.40	57.14	2179.93	38308.58	1.11
AUC∞ (hr *pg/ml)	12964.85	56.08	3007.80	42524.92	11825.04	56.39	2582.15	39799.48	1.10
Cmax (pg/ml)	1291.04	61.67	275.00	5560.00	1181.49	56.35	222.00	3700.00	1.09
Tmax* (hr)	4.50	.	1.00	12.00	4.50	.	2.50	15.00	1.00
Kel (hr^{-1})	0.13	17.20	0.07	0.18	0.12	20.82	0.06	0.18	1.08
T1/2 (hr)	5.60	19.05	3.85	9.90	6.12	23.93	3.85	11.55	0.91

* Tmax values are presented as median, range

Table 16. Geometric Means and 90% Confidence Intervals - Firm Calculated

Budesonide controlled release capsule 3 x 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study, Study No. 10716217						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC0-t (hr *pg/ml)	10918.46	79	9854.16	79	1.1080	1.0558 – 1.1628
AUC∞ (hr *pg/ml)	11254.33	79	10310.44	79	1.0916	1.0424 – 1.1430
Cmax (pg/ml)	1115.29	79	1006.96	79	1.1076	1.0360 – 1.1842

Table 17. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Budesonide controlled release capsule 3 x 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10716217							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	10916.83	79	9851.42	79	1.11	105.60	116.28
AUC∞ (hr *pg/ml)	11253.65	79	10304.85	79	1.09	104.29	114.35
Cmax (pg/ml)	1115.29	79	1006.96	79	1.11	103.60	118.42

Table 18. Additional Study Information, Fasting Study No. 10716217

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CONTINU2	
Reason(s) for Selecting Above SAS Program Macro	Please see comment below the table	
Root mean square error, AUC0-t	0.1818	
Root mean square error, AUC∞	0.1738	
Root mean square error, Cmax	0.2523	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	NA	NA
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	NA	NA
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
Cmax as first time point	1 subject (56, period 1, test treatment)	None
Were the subjects dosed as more than one group?	No	

Ratio of AUC0-t/AUC∞[12]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	79	0.97	0.90	1.00
Reference	79	0.96	0.78	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Subject 13, treatment 2, reported a ratio of 0.78. The half life of drug elimination in this subject was 12.58. The sampling time of 36 hrs (~3 half-lives) is not sufficient to capture the entire elimination phase.			

Was the fasting bioequivalence study acceptable?
Yes.

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

(If Tmax difference is considered substantial, include a table of individual Tmax values in rank order above.)

[12] See individual test to reference ratios of PK Parameters in SAS Output.

1. The reviewer used the SAS code: ContinuII for the statistical analysis to verify the statistical results submitted by the firm. The reviewer agrees with the firm's selection of time points for the elimination phase.

2. The observed subject variability as observed with the root mean square error for the AUC and Cmax was less than 30%. Hence this is not a highly variable drug.

3. The median Tmax of the Test product is the same as that of the Reference product.

4. One subject exhibited AUC ratio of 0.78 (Subject 13, Reference treatment), an additional analysis was performed excluding the data from this subject. The outcome of the study was unaffected. For details see table below:

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	10944.50	9931.63	1.10	105.04	115.61
LAUCI	11274.36	10359.66	1.09	103.91	113.99
LCMAX	1116.24	1016.74	1.10	102.76	117.29

5. One subject reported the first measurable concentration as Cmax (subject 56, period 1, Test treatment). An additional analysis was performed excluding the data from this subject. The outcome of the study was unaffected. For details see table below:

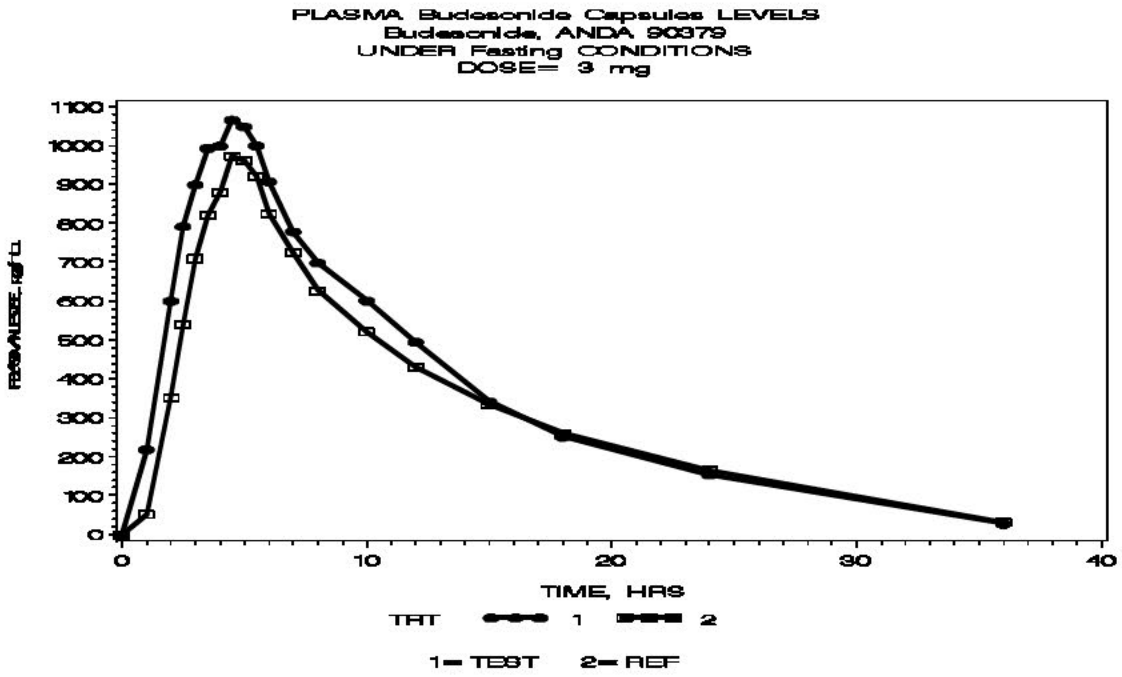
	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	10953.41	9845.24	1.11	106.00	116.77
LAUCI	11294.16	10301.49	1.10	104.69	114.82
LCMAX	1115.70	1003.06	1.11	103.98	118.98

6. The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of Budesonide are within the acceptable BE limits of 80.00% - 125.00%.

Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=79)		Reference (n=79)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	218.09	109.69	51.19	195.24	4.26
2.00	599.85	77.86	352.78	115.76	1.70
2.50	791.47	84.08	539.26	86.26	1.47
3.00	899.16	83.95	709.39	78.39	1.27
3.50	993.09	72.25	822.26	70.51	1.21
4.00	998.49	63.98	880.97	65.28	1.13
4.50	1065.41	61.32	973.53	59.12	1.09
5.00	1048.39	57.13	960.65	52.41	1.09
5.50	999.47	55.52	920.29	49.94	1.09
6.00	906.89	49.52	824.30	48.30	1.10
7.00	778.66	47.21	726.04	60.37	1.07
8.00	698.16	49.44	627.48	70.29	1.11
10.00	601.06	74.86	520.49	78.03	1.15
12.00	494.67	76.63	431.61	66.74	1.15
15.00	341.68	83.50	335.18	78.26	1.02
18.00	251.10	82.64	260.00	80.34	0.97
24.00	153.03	104.56	166.12	93.53	0.92
36.00	26.81	133.24	30.46	119.44	0.88

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study[13]



[13] For individual subjects' concentration vs time profile, please see SAS Output

4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 20. Study Information

Study Number	10716218
Study Title	A Relative Bioavailability Study of Two Budesonide 3 mg Controlled Release Capsule Formations Under Non-Fasting Conditions
Clinical Site (Name & Address)	Novum Pharmaceutical Research Services 3320 Walnut Bend Lane Houston, Texas 77042-4712 832-251-8100
Principal Investigator	Soran Hong, M.D.
Dosing Dates	Period I: 10/21/07 Period II: 10/28/07
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	11/21/2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Long Term Freezer stability has been established at 525 days @ -20°C 4 Days Sample collection started on 11/5/07 and was completed on 11/8/07

Table 21. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Budesonide Enteric Coated Capsule	Entocort® EC
Manufacturer	Barr Laboratories, Inc.	AstraZeneca
Batch/Lot No.	800206	NC0077
Manufacture Date	3/15/2007	N/A
Expiration Date	N/A	11/30/09
Strength	3mg	3mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4) capsules	N/A
Production Batch Size	capsules	N/A
Potency (Assay)	3mg	3mg
Content Uniformity (expressed as	102.7%, 0.1%	102.6, 0.4%

mean, %CV or per USP)		
Dose Administered	3mg	3mg
Route of Administration	Oral	Oral

Was the drug product administered per labeling?	Yes, Entocort EC capsules should be swallowed whole and not chewed or broken.
Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form?	Yes, (b) (4) capsules.

Table 22. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	**Enrolled: 24** **Dosed: 24** **Completed: 23**[14] **Samples Analyzed: 23** **Data Analyzed: 23**
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme (Sequence of T and R)	AB: 01, 04, 05, 07, 09, 11, 13, 15, 17, 19, 22 and 24. BA: 02, 03, 06, 08, 10, 12, 14, 16, 18, 20, 21, and 23.
Blood Sampling Times	Pre-dose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 15, 18, 24, and 36 hours.
Blood Volume Collected/Sample	The total volume of blood collected over the duration of the study for pharmacokinetic sampling and safety testing for each subject was approximately 316 mL over an approximate 5 week period (including the 28-day screening window).
Anticoagulant Used	K3 EDTA.

[14] On 10/26/07, subject 14 tested positive for cocaine at Period 2 check-in. This subject was dropped from the study. This participant refused end-of-study evaluations.

Blood Sample Processing & Storage (include storage temperature)	In each period, 7 mL venous blood was collected in K3 EDTA Vacutainers prior to dosing and at the times as mentioned in blood sampling times. The samples were labeled at the time of collection with a unique code number, and within 60 minutes of collection, were centrifuged at approximately 2700 rpm for 15 minutes at 4°C. The resulting plasma was separated into 2 approximately equal aliquots and placed in the freezer within 120 minutes of blood collection. Pre-dose samples were collected up to one hour before dosing. All plasma samples were stored frozen to at least -21°C. Plasma samples for all subjects completing both periods of the study were shipped to (b) (4)
IRB Approval	The protocol was reviewed and approved by the (b) (4) Independent Institutional Review Board (b) (4) on 09/11/07, prior to study commencement.
Informed Consent	The informed consent form was reviewed and approved by the (b) (4) Independent Institutional Review Board (b) (4) on 09/11/07, prior to study commencement.
Length of Fasting	Standardized light, low fat meals were provided at 34, 24, 20, 15 and 10.5 hours prior to a standard FDA high fat breakfast that was served 30 minutes prior to dosing with budesonide. No food or beverages (except water) were permitted during the 10 hour fasting period leading up to the standardized breakfast.
Length of Confinement	Subjects were confined at the clinical facility from at least 34 hours prior to dosing until after the 24 hour blood collection.
Safety Monitoring	The subjects were monitored throughout the study for any adverse experiences. Adverse events were collected through both solicited and unsolicited means and were subsequently coded in tabular form using the MeDRA Version 8.0 adverse event dictionary. The subjects were encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each adverse event was determined by the clinic staff based on observation and questioning of the subject. The Investigator judged the relationship of the event to the study treatments. None of the adverse events experienced by the subjects during this study were judged as serious.

Standard FDA Meal Used?	Yes. The standardized breakfast consisted of two eggs fried in butter, two strips of bacon, four ounces of has brown potatoes, two slices of toast with butter, and eight ounces of whole milk. This high fat/high calorie breakfast contained approximately 150 calories derived from protein, 250 calories derived from carbohydrate, and 500 calories derived from fat.

If No, then meal components and composition is listed in the tables below

Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study: Not applicable

Composition	Percent	Kcal
Fat	N/A	
Carbohydrate		
Protein		
Total		

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study: Not applicable

Component	Kcal
Chicken tikka (presented as an example only)	
etc.	

Was the study design used for the fed BE study acceptable?	YES

Comments on Study Design:

The Study design is acceptable.

4.1.2.2 Clinical Results

Table 23. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 10716218			
		Treatment Groups	
		Test Product N = 23	Reference Product N = 23
Age (years)	Mean ± SD	31.30 ± 8.82	31.30 ± 8.82
	Range	21 - 56	21 - 56
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	21 (91.30%)	21 (91.30%)
	41 – 64	2 (8.70%)	2 (8.70%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	17 (73.91%)	17 (73.91%)
	Female	6 (26.09%)	6 (26.09%)
Race	Asian	0 (0%)	0 (0%)
	Biracial	0 (0%)	0 (0%)
	Black	18 (78.26%)	18 (78.26%)
	Caucasian	5 (21.74%)	5 (21.74%)
Ethnicity	Yes	3 (13.04%)	3 (13.04%)
	No	20 (86.96%)	20 (86.96%)
Weight (Lbs)	Mean ± SD	164.26 ± 24.82	164.26 ± 24.82
	Range	112 - 222	112 - 222
BMI (Kg/m^2)	Mean ± SD	24.57 ± 3.02	24.57 ± 3.02
	Range	19.1 – 29.9	19.1 – 29.9
Tobacco User	Yes	1 (4.35%)	1 (4.35%)
	No	22 (95.65%)	22 (95.65%)

Table 24. Dropout Information, Fed Bioequivalence Study

Study 10716218				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
14	On 10/26/07, this subject (b) (6) tested positive for cocaine at Period 2 check-in. This subject was dropped from the study. This participant refused end-of-study evaluations.	II	No	N/A

Table 25. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event	Bioequivalence Study Study No. 10716218	
	Test A N (%)	Reference B N (%)
Investigations		
Blood glucose increased	0 (0%)	1 (4.17%)
Respiratory, thoracic and mediastinal Disorders		
Nasal Congestion	0 (0%)	1 (4.17%)
TOTAL	**0 (0%)**	**2 (8.33%)**

Do any of the adverse events require statistical analysis consideration (e.g. vomiting)?
No

If yes, does the time exceed the Tmax limit according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Prodcuts*?
Not applicable.

Was the adverse event profile observed during the fasting bioequivalence study the same for the test and reference product?
Yes, the adverse event profile observed during the fasting bioequivalence study was the same for the test and reference products.

Table 26. Protocol Deviations, Fed Bioequivalence Study

Study No. 10716218		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
The protocol states that all doses are administered with 240 ml of room temperature water. Subject 24 (b) (6), required an additional 240 ml of water to swallow the capsules during Period I dosing. In order to maintain consistent water intake in Periods 1 and 2, the subject was also provided with the additional 240 ml of water in Period 2 of the study. The Principal Investigator determined that this amount of water would not compromise the subject's safety or the integrity of the data. This subject's samples were sent for analysis.	24	24

Did dropouts/adverse events/protocol deviations affect the study outcome?
No.

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. Twenty-four (24) subjects were enrolled in the study, and 23 subjects completed the study. On 10/26/07, subject 14 tested positive for cocaine at Period 2 check-in.

This subject was dropped from the study. This participant refused end-of-study evaluations.

2. Per the firm's report, "A total of 2 adverse events (0, Test; 2, Reference) were reported by 2 of the 24 subjects who participated in this study. All adverse events were mild and resolved spontaneously, with the exception of 1 abnormal post study laboratory evaluation. The subject exhibiting this abnormal value is considered lost to follow-up".

3. There was one protocol deviation observed as stated above in subject 24 which was in regards to additional 240 ml of water required to swallow the capsule. This deviation is not likely to have an impact on the outcome of the study.

4.1.2.3 Bioanalytical Results

Table 24. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. 10716218 Analyte Name Budesonide								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	10.0	18.0	30.0	100	300	800	2000	2500
Inter day Precision (%CV)	6.96	5.92	6.13	4.53	4.37	4.46	3.53	3.80
Inter day Accuracy (%Actual)	103	98.4	99.7	98.9	101	99.6	99.5	100
Linearity	(Range of R2 values) 0.9975 to 0.9998							
Linearity Range (pg/mL)	10.0 to 2500							
Sensitivity/LOQ (pg/mL)	10.0							

Parameter	**Quality Control Samples**				
Concentration (pg/mL)	25.0	50.0	150	500	1880
Inter day Precision (%CV)	5.91	6.47	3.79	4.07	4.52
Inter day Accuracy (%Actual)	98.5	100	102	99.4	102
Number of Acceptable Runs	13				
Number of Rejected Runs (Run ID, volume/page location)	There were no rejected runs.				
If sample and QC diluted during study, specify all dilution factors	For analytical runs which contained diluted subject samples, the appropriate level quality control pool was diluted and analyzed in a similar manner to validate the dilution of study samples. The samples were diluted 2 fold to 5-fold.				
Was 100% of raw numerical data submitted?	Yes.				

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes.
Were chromatograms serially or randomly selected?	serially
Were the chromatograms submitted by the firm acceptable?	Yes

Was the Study Assay Validation acceptable?
Acceptable.

Summary/Conclusions, Study Assays:

Per the firm, "to demonstrate reproducible quantitation of incurred subject samples, at least 10% of the study samples were reassayed as incurred sample repeats. The repeat values were used for comparison purposes and are included in the analytical report but not used in determining the final reported value. Normal assessment of the result from the initial analysis was made and the repeat result was compared against the reportable result. Incurred sample repeats were considered acceptable if the original and reassay values from two-thirds of the repeated samples had a relative percent difference of ≤ 30%."

Table 25. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Conduct of an Analytical Study

Table 26. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The firm's repeat analysis is acceptable. For additional details, please refer to section 3.6: In Vivo Studies.

4.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 2 and Figure 3

Fed Bioequivalence Study, Study No. 10716218									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *pg/ml)	15889.90	57.81	6708.28	50313.28	17220.05	66.81	5114.55	53958.48	0.92
AUC∞ (hr *pg/ml)	16143.16	57.18	7580.09	50874.81	17502.49	66.06	6124.55	54647.71	0.92
Cmax (pg/ml)	2387.39	66.76	750.00	8090.00	2549.17	69.97	701.00	7930.00	0.94
Tmax* (hr)	6.00	.	3.00	10.00	6.00	.	3.00	12.00	1.00
Kel (hr^{-1})	0.14	14.68	0.10	0.19	0.14	14.98	0.10	0.19	0.97
T1/2 (hr)	5.17	15.49	3.65	6.93	5.01	15.03	3.65	6.93	1.03

* Tmax values are presented as median, range

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

Budesonide controlled release capsule 3 x 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study, Study No. 10716218						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC0-t (hr *pg/ml)	14179 36	23	14702.94	23	0.9644	0.9104 – 1.0216
AUC∞ (hr *pg/ml)	14465.78	23	15047.55	23	0.9613	0.9103 – 1.0153
Cmax (pg/ml)	2039.61	23	2133.08	23	0.9562	0.8639 – 1.0583

Table 32. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Budesonide controlled release capsule 3 x 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study, Study No. 10716218							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *pg/ml)	14179.51	23	14702.81	23	0.96	91.04	102.16
AUC∞ (hr *pg/ml)	14467.95	23	15045.22	23	0.96	91.04	101.58
Cmax (pg/ml)	2039.61	23	2133.08	23	0.96	86.39	105.83

Table 33. Additional Study Information, Fed Study No.

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CONTINU2	
Reason(s) for Selecting Above SAS Program Macro	Please see comment below the table	
Root mean square error, AUC0-t	0.1135	
Root mean square error, AUC∞	0.1078	
Root mean square error, Cmax	0.1998	
	Test	**Reference**
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC∞	NA	NA
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC∞	NA	NA
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	None	None
Cmax at the first time point	No	
Were the subjects dosed as more than one group?	NA	

Ratio of AUC0-t/AUC∞[15]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	23	0.98	0.88	1.00
Reference	23	0.98	0.84	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	Not applicable			

Was the fed bioequivalence study acceptable?
Yes.

Comments on SAS Program selected, Subject variability, any Tmax differences (if applicable), Pharmacokinetic and Statistical Analysis:

(If Tmax difference is considered substantial, include a table of individual Tmax values in rank order above.)

1. The reviewer used the SAS code: ContinuII for the statistical analysis to verify the statistical results submitted by the firm. The reviewer agrees with the firm's selection of time points for the elimination phase.

2. The observed subject variability as observed with the root mean square error for the AUC and Cmax was less than 30%. Hence this is not a highly variable drug.

3. There have been no Tmax differences observed.

[15] See individual test to reference ratios of PK Parameters in SAS Output.

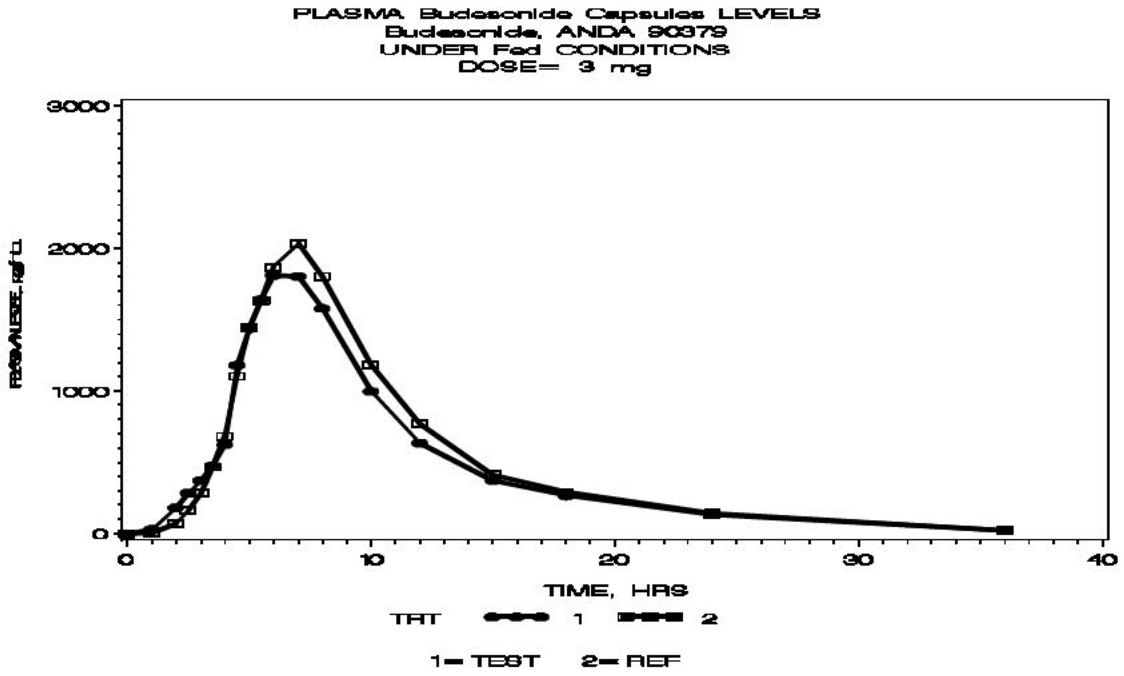
4. The 90% confidence intervals for log-transformed AUC_{0-t}, AUC_{∞} and C_{max} of Budesonide are within the acceptable BE limits of 80.00% - 125.00%.

APPEARS THIS WAY ON ORIGINAL

Table 34. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=23)		Reference (n=23)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	27.96	155.71	4.57	209.79	6.12
2.00	180.21	136.70	71.22	149.91	2.53
2.50	283.48	127.15	166.00	137.55	1.71
3.00	372.25	120.69	285.99	120.18	1.30
3.50	475.47	105.03	467.75	109.54	1.02
4.00	623.71	87.55	684.59	108.32	0.91
4.50	1179.95	85.61	1106.29	95.19	1.07
5.00	1440.67	78.66	1448.57	78.14	0.99
5.50	1641.61	76.20	1634.71	80.65	1.00
6.00	1812.04	88.68	1870.04	92.38	0.97
7.00	1803.39	87.90	2030.87	90.51	0.89
8.00	1578.26	74.72	1801.13	79.97	0.88
10.00	997.26	64.96	1180.57	76.46	0.84
12.00	635.65	67.61	770.74	73.51	0.82
15.00	373.00	57.11	412.57	65.64	0.90
18.00	265.10	60.20	288.30	62.62	0.92
24.00	134.64	70.78	137.87	73.34	0.98
36.00	22.91	82.58	24.35	90.53	0.94

Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	Not applicable
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	Not applicable
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	YES
If no, are they all above/within IIG (per day) limits?	Not applicable
If no, are additional data or Pharm/Tox consult necessary?	Not applicable
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	YES
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	Not applicable
Are all strengths of the RLD product dose-proportional?	Not applicable
Are all strengths of the test formulation acceptable	YES

Reviewer's comments[16],[17]**:**

1. All excipients fall below the IIG limits for this route of administration. The recommended total daily intake of Budesonide Enteric-Coated Capsule is 9 mg, which is equivalent to three capsules per day. The firm notes the following issues pertaining to the components.

2. (b) (4)

3.

[16] DARRTS Search: ANDA 090379; REV-QUALITY-03 (General Review); Final Date: 12/07/2009.
[17] DARRTS Search: ANDA 090379; REV-RPM-03 (Filing Review); Final Date: 04/07/2008.

4. All components present in the black ink have been used in approved drug products.

APPEARS THIS WAY ON ORIGINAL

4.3 Dissolution Data

Dissolution Review Path	DARRTS Search; ANDA 090379; REV-BIOEQ-02 (Dissolution Review): Final Date: 07/25/2008.

Table 33. Dissolution Data (TO BE INCLUDED IN ECTD TABLE LIST)

Dissolution Conditions	**Apparatus:**	Apparatus II (paddles) with capsule sinker
	Sinker	Yes
	Speed of Rotation:	75 rpm
	Medium:	Medium 1: 0.01 N HCl (first 2 hours); Medium 2: pH 7.5 phosphate solution (1-6 hours)
	Volume:	1000 mL
	Temperature:	37°C ± 5°C
Firm's Proposed Specifications	Less than (b) (4)% in 0.1 N HCl in 2 hrs and in pH 4.5 phosphate buffer (up to 8 hours)	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc., 223 Quaker Road, Pomona, NY 10970	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**						**Study Report Location**
						2 hours	**1 hour**	**2 hours**	**4 hours**	**6 hours**	**8 hours**	
						Medium 1: 0.01N HCl (First 2 hours) Acid Stage	**Medium 2: pH 7.5 phosphate solution (2-10 hours) (Buffer Stage)**					
ARD_RPT - 3041	9/28/07	Test: Budesonide Enteric Coated Capsule Lot No. 800206 Mfr Date: 9/9/07	3mg Capsule	12	Mean	1	37	56	77	88	93	Barr Laboratories, Inc.
					Range		(b) (4)					
					%CV	0.0	6.4	5.6	3.2	2.4	2.3	
	3/28/07	Reference: Entocort EC Lot No. NC0077 Exp. Date: 11/30/09	3mg Capsule	12	Mean	1	53	73	92	97	98	
					Range		(b) (4)					
					%CV	0.0	4.4	2.8	1.6	2.3	2.7	

Note: The calculated F2 value for this product (test vs reference) is 43.85.

Figure 5. Dissolution Profiles

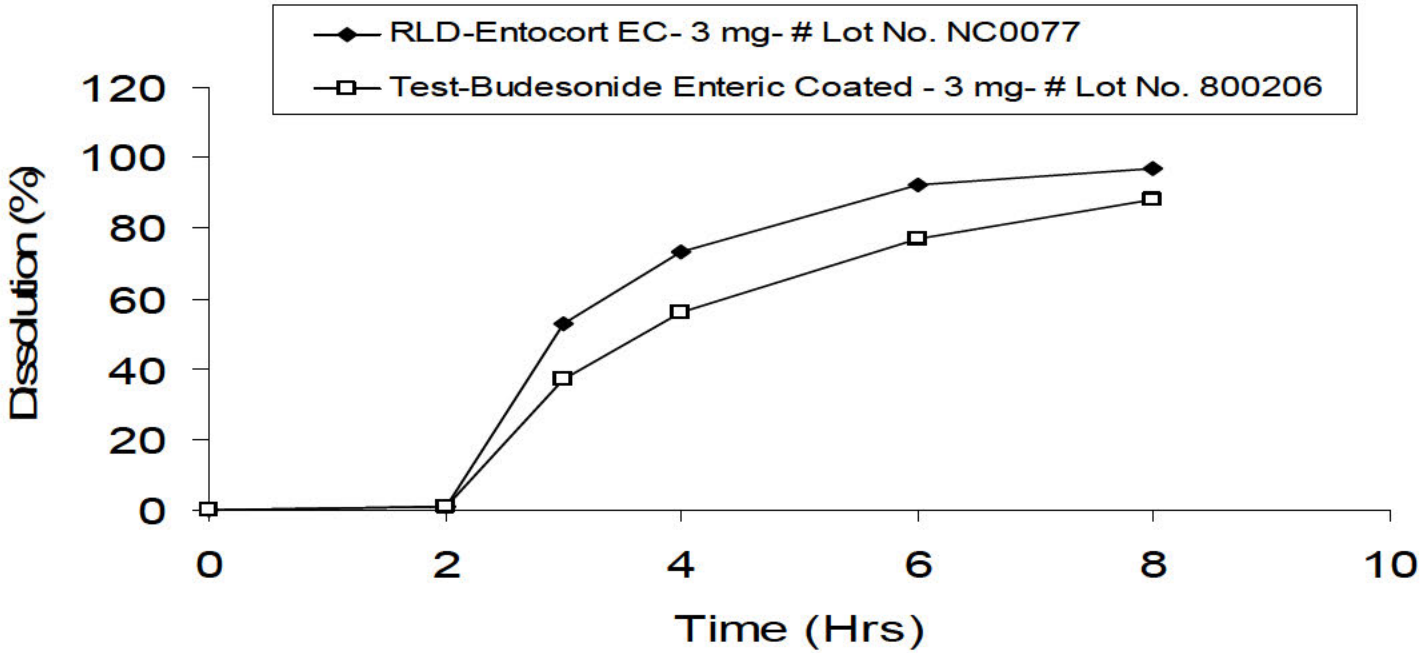


Table 2.2: Dissolution data in 0.1 N HCl (pH 1.2)

Sample No.	Biobatch: 800206	RLD: NC0077
	% Dissolved - 2 hours	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean	**1**	**1**
High	(b) (4)	
Low		

Table 2.3: Dissolution data in pH 4.5 buffer

	Biobatch: 800206					RLD: NC0077				
Time (hour)	1	2	4	6	8	1	2	4	6	8
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	**2**	**3**	**4**	**6**	**7**	**0**	**1**	**2**	**2**	**3**
High	(b) (4)									
Low										

Table 2.4: Dissolution data in pH 6.8 Buffer

	Biobatch: 800206					RLD: NC0077				
Time (hour)	1	2	4	6	8	1	2	4	6	8
1	[redacted] (b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	**34**	**51**	**71**	**83**	**90**	**45**	**70**	**91**	**97**	**98**
High	[redacted] (b) (4)									
Low										
RSD	5.9	4.3	2.7	2.6	2.1	4.0	2.6	2.1	3.1	3.0

4.4 Division of Scientific Investigation (DSI) Inspection Report Review

4.4.1 Summarization of the DSI Inspection of Clinical Site

The following is the history of the inspections held for the clinical site: Novum Pharmaceutical Research Services, 3320 walnut bend lane, Houston, Texas 77042-4712.

BE inspections at Novum:

1. ANDA 78-376, 7/25/07, NAI
2. ANDA 78-830, 7/25/07, NAI
3. (b) (4)
4. NDA 22-439, 2/15/10, NAI

Since the DSI findings of these inspections are all categorized as NAI, the DSI report were not reviewed in this report.

4.4.2 Summarization of the DSI Inspection of Analytical Site

The following is the history of the inspections held for the analytical site: (b) (4)

BE inspections at (b) (4)

1. (b) (4) NDA 21-875, (b) (4)
2. (b) (4)
3. (b) (4) ANDA 77-728 (b) (4)
4. ANDA 77-693
5. , NDA 22-113,
6. (b) (4)
7. (b) (4), NDA 21-227, (b) (4)
8. (b) (4)
9. (b) (4), NDA 201-739, (b) (4)
10. (b) (4)

The outcome of the BE inspections (b) (4) are reviewed here. Study dates for ANDA 090379 are from 10/07/07 to 11/21/07.

NDA 021875:

At the request of HFD-120, the Division of Scientific Investigations conducted an audit of the following bioequivalence studies[18]*:*

[18] DARRTS Search: NDA 021875; CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review); Final Date: (b) (4).

Following this page, 3 Pages Withheld in Full as (b)(4)

Impact on current ANDA:
For the current study for ANDA 090379, samples were received frozen and in good condition from Novum PRS, Houston, Texas. Sample analysis was performed using the original sample tubes. The samples were stored frozen at approximately -20°C. The long-term freezer stability has been established for 525 days at -20°C. Hence, the finding stated above will not have any impact on the outcome of the current study.

4.5 Detailed Regulatory History (If Applicable)

APPEARS THIS WAY ON ORIGINAL

4.6 Consult Reviews

APPEARS THIS WAY ON ORIGINAL

4.7 SAS Output

4.7.1 Fasting Study Data

90379 Fasting REVIEWER VERIFIED CONCENTRATION DATASET

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
1	1	2	1	B	1	0	0.0	10.4	11.5	24.8	72.6	267.0	979.0	1510	1660	1510	1170	814	611.0	480.0	385.0	246.0	170.0	28.8
2	1	2	2	A	1	0	57.1	108.0	147.0	237.0	254.0	244.0	289.0	395	485	631	765	1030	1320.0	1000.0	667.0	474.0	351.0	58.6
3	2	1	1	A	1	0	266.0	803.0	904.0	975.0	951.0	923.0	801.0	689	711	765	587	467	388.0	344.0	271.0	154.0	160.0	26.4
4	2	1	2	B	1	0	0.0	114.0	573.0	1030.0	1230.0	1110.0	1140.0	1110	956	894	688	534	385.0	394.0	237.0	197.0	102.0	21.3
5	3	2	1	B	1	0	0.0	17.5	155.0	333.0	603.0	649.0	784.0	882	884	746	569	472	361.0	347.0	186.0	143.0	76.9	12.2
6	3	2	2	A	1	0	32.1	156.0	211.0	270.0	385.0	496.0	614.0	722	729	789	762	754	704.0	507.0	261.0	172.0	90.6	11.0
7	4	1	1	A	1	0	567.0	1350.0	1510.0	1740.0	1570.0	1440.0	1340.0	1350	1280	1180	868	760	495.0	368.0	198.0	135.0	53.9	0.0
8	4	1	2	B	1	0	594.0	1310.0	1440.0	1440.0	1330.0	1320.0	1080.0	998	870	838	624	570	377.0	323.0	180.0	132.0	55.4	0.0
9	5	1	1	A	1	0	48.3	214.0	250.0	436.0	823.0	1120.0	1460.0	1320	1190	1150	963	937	1000.0	807.0	666.0	560.0	274.0	38.3
10	5	1	2	B	1	0	0.0	308.0	605.0	1060.0	1310.0	1370.0	1420.0	1420	1170	1350	1090	1000	914.0	749.0	868.0	772.0	454.0	92.9
11	6	2	1	B	1	0	0.0	11.3	15.6	124.0	491.0	780.0	1060.0	1150	1130	1030	991	983	972.0	840.0	871.0	678.0	491.0	112.0
12	6	2	2	A	1	0	81.9	538.0	892.0	1040.0	1080.0	1030.0	1160.0	1080	1110	990	915	1480	1530.0	1330.0	1020.0	787.0	576.0	101.0
13	7	2	1	B	1	0	38.7	975.0	1470.0	2050.0	2420.0	2530.0	2410.0	2410	2140	1720	1340	1130	926.0	629.0	369.0	231.0	116.0	13.8
14	7	2	2	A	1	0	319.0	1460.0	1800.0	1990.0	2100.0	2040.0	1910.0	1720	1450	1210	1010	892	717.0	564.0	379.0	263.0	144.0	24.9
15	8	1	1	A	1	0	46.8	197.0	354.0	339.0	359.0	338.0	415.0	445	474	550	385	406	284.0	226.0	187.0	203.0	139.0	20.5
16	8	1	2	B	1	0	0.0	21.2	40.9	150.0	187.0	252.0	358.0	451	484	559	498	430	385.0	497.0	539.0	443.0	326.0	23.1
17	9	2	1	B	1	0	484.0	2290.0	2400.0	2870.0	2480.0	2730.0	2090.0	2130	2020	1840	1710	1210	1200.0	1010.0	657.0	533.0	265.0	31.1
18	9	2	2	A	1	0	16.4	1090.0	4690.0	5560.0	4850.0	3670.0	4070.0	3530	3210	2650	2000	1580	1080.0	934.0	561.0	371.0	179.0	26.2
19	10	1	1	A	1	0	448.0	1040.0	1260.0	1410.0	1470.0	1600.0	1660.0	1540	1250	1180	825	799	518.0	358.0	224.0	157.0	60.1	0.0
20	10	1	2	B	1	0	0.0	646.0	1310.0	1680.0	2130.0	1960.0	1950.0	1540	1380	1210	916	803	514.0	385.0	275.0	169.0	87.1	16.1
21	11	2	1	B	1	0	93.6	517.0	723.0	1020.0	1100.0	1340.0	1350.0	1080	871	715	625	614	448.0	441.0	366.0	339.0	158.0	31.7
22	11	2	2	A	1	0	192.0	612.0	802.0	823.0	948.0	1120.0	1570.0	1520	1320	1150	944	785	677.0	499.0	475.0	395.0	232.0	48.2

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
23	12	1	1	A	1	0	309.0	1100.0	1330.0	1390.0	1570.0	1570.0	1540.0	1530	1300	1210	1020	799	489.0	453.0	299.0	182.0	85.4	0.0
24	12	1	2	B	1	0	17.0	430.0	912.0	1110.0	1240.0	1290.0	1700.0	2040	1820	1450	1070	772	580.0	515.0	331.0	179.0	102.0	11.8
25	13	1	1	A	1	0	405.0	791.0	850.0	898.0	772.0	762.0	646.0	654	609	553	479	424	325.0	258.0	138.0	111.0	60.8	0.0
26	13	1	2	B	1	0	84.4	273.0	350.0	371.0	396.0	424.0	457.0	427	417	340	317	300	241.0	208.0	141.0	117.0	85.5	0.0
27	14	2	1	B	1	0	0.0	0.0	10.9	31.7	39.9	51.3	132.0	197	242	309	310	318	212.0	153.0	101.0	79.3	36.5	0.0
28	14	2	2	A	1	0	0.0	104.0	217.0	331.0	376.0	344.0	312.0	382	377	313	224	187	119.0	81.5	51.7	36.2	20.1	.
29	15	1	1	A	1	0	142.0	545.0	622.0	671.0	674.0	733.0	730.0	636	597	641	984	962	546.0	332.0	211.0	147.0	66.3	0.0
30	15	1	2	B	1	0	0.0	191.0	356.0	381.0	424.0	431.0	555.0	641	680	609	505	473	352.0	295.0	171.0	148.0	67.2	0.0
31	16	2	1	B	1	0	0.0	60.1	126.0	160.0	180.0	212.0	240.0	272	258	271	246	215	207.0	270.0	208.0	155.0	86.8	0.0
32	16	2	2	A	1	0	161.0	569.0	710.0	638.0	695.0	712.0	639.0	602	638	584	448	344	280.0	241.0	158.0	105.0	41.7	0.0
33	17	2	1	B	1	0	0.0	167.0	209.0	226.0	244.0	317.0	493.0	501	495	438	371	299	250.0	212.0	123.0	82.3	47.4	0.0
34	17	2	2	A	1	0	0.0	66.7	121.0	168.0	226.0	249.0	321.0	470	548	538	413	425	459.0	329.0	200.0	118.0	55.2	0.0
35	18	1	1	A	1	0	49.6	363.0	486.0	609.0	731.0	701.0	607.0	569	476	442	371	355	329.0	354.0	278.0	246.0	170.0	27.5
36	18	1	2	B	1	0	42.3	164.0	249.0	245.0	267.0	311.0	282.0	295	302	289	281	275	249.0	275.0	335.0	331.0	224.0	37.1
37	19	1	1	A	1	0	94.3	231.0	302.0	316.0	321.0	329.0	361.0	348	380	381	330	253	158.0	141.0	87.7	81.0	35.9	0.0
38	19	1	2	B	1	0	0.0	0.0	16.6	33.5	132.0	243.0	350.0	395	385	386	392	321	251.0	192.0	190.0	166.0	103.0	11.8
39	20	2	1	B	1	0	69.2	428.0	647.0	689.0	683.0	677.0	710.0	683	670	627	510	581	493.0	404.0	277.0	190.0	87.5	13.7
40	20	2	2	A	1	0	50.2	264.0	386.0	429.0	693.0	719.0	817.0	890	788	714	643	602	672.0	579.0	323.0	254.0	116.0	14.8
41	21	2	1	B	1	0	66.1	478.0	546.0	747.0	788.0	890.0	1020.0	1230	1420	1220	1170	1170	1360.0	1260.0	1090.0	977.0	773.0	170.0
42	21	2	2	A	1	0	25.1	112.0	129.0	261.0	679.0	1040.0	1250.0	1580	1750	1690	1590	1550	1610.0	1570.0	1250.0	951.0	609.0	108.0
43	22	1	1	A	1	0	102.0	582.0	906.0	881.0	1110.0	1390.0	1450.0	1350	1280	1020	987	914	685.0	487.0	274.0	224.0	154.0	25.4
44	22	1	2	B	1	0	0.0	94.1	147.0	289.0	733.0	1260.0	2770.0	2290	2010	1720	1160	1000	720.0	541.0	289.0	214.0	138.0	33.0
45	23	2	1	B	1	0	15.6	122.0	186.0	234.0	421.0	596.0	899.0	1100	1340	1300	1040	980	642.0	498.0	276.0	225.0	119.0	19.4
46	23	2	2	A	1	0	82.1	319.0	627.0	895.0	1090.0	1180.0	1330.0	1520	1490	1300	1180	1070	834.0	604.0	410.0	300.0	172.0	29.7
47	24	1	1	A	1	0	244.0	770.0	942.0	1280.0	1250.0	1030.0	795.0	802	714	749	611	604	499.0	483.0	381.0	378.0	353.0	25.7
48	24	1	2	B	1	0	0.0	57.3	163.0	177.0	206.0	331.0	468.0	760	926	922	985	937	856.0	587.0	317.0	231.0	156.0	26.3
49	25	1	1	A	1	0	272.0	805.0	823.0	945.0	863.0	895.0	888.0	824	846	808	730	691	489.0	389.0	301.0	199.0	98.9	12.5
50	25	1	2	B	1	0	0.0	24.8	181.0	406.0	496.0	521.0	777.0	836	844	841	727	612	538.0	569.0	415.0	256.0	119.0	10.6
51	26	2	1	B	1	0	70.8	478.0	698.0	731.0	744.0	757.0	771.0	791	780	650	581	478	377.0	361.0	278.0	208.0	145.0	21.2

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
52	26	2	2	A	1	0	74.3	608.0	1090.0	1500.0	1670.0	1820.0	2040.0	1970	1800	1490	1150	1100	773.0	574.0	342.0	301.0	128.0	22.0
53	27	2	1	B	1	0	112.0	568.0	724.0	707.0	744.0	753.0	839.0	1050	1000	843	714	556	435.0	339.0	244.0	143.0	83.6	0.0
54	27	2	2	A	1	0	36.8	166.0	348.0	542.0	850.0	933.0	1150.0	1230	1340	1160	1100	812	619.0	750.0	395.0	245.0	111.0	11.2
55	28	1	1	A	1	0	74.9	186.0	329.0	418.0	471.0	512.0	650.0	750	710	716	645	717	746.0	818.0	338.0	269.0	141.0	28.9
56	28	1	2	B	1	0	20.5	359.0	508.0	576.0	528.0	488.0	547.0	643	661	654	586	490	492.0	436.0	257.0	202.0	133.0	39.0
57	29	1	1	A	1	0	148.0	534.0	550.0	598.0	547.0	443.0	412.0	347	339	315	256	205	128.0	88.8	47.1	33.2	17.0	0.0
58	29	1	2	B	1	0	0.0	36.3	97.4	178.0	244.0	304.0	403.0	374	398	408	318	244	141.0	102.0	52.3	34.9	16.8	0.0
59	30	2	1	B	1	0	63.1	226.0	404.0	425.0	431.0	376.0	351.0	361	406	350	321	268	208.0	229.0	206.0	179.0	101.0	54.7
60	30	2	2	A	1	0	138.0	418.0	470.0	482.0	519.0	451.0	462.0	482	486	477	451	387	325.0	363.0	255.0	207.0	124.0	32.1
61	31	1	1	A	1	0	18.8	73.6	79.4	172.0	286.0	354.0	416.0	528	577	595	538	804	548.0	403.0	243.0	149.0	71.5	0.0
62	31	1	2	B	1	0	0.0	412.0	616.0	603.0	690.0	694.0	718.0	778	743	675	521	462	417.0	325.0	191.0	138.0	64.3	11.1
63	32	2	1	B	1	0	345.0	1690.0	1700.0	2010.0	1830.0	1860.0	1820.0	1750	1460	1270	1030	865	587.0	492.0	328.0	307.0	134.0	26.2
64	32	2	2	A	1	0	278.0	977.0	1420.0	1600.0	1790.0	1890.0	1890.0	1670	1430	1450	1060	860	819.0	764.0	396.0	286.0	125.0	17.8
65	33	2	1	B	1	0	0.0	112.0	202.0	227.0	252.0	262.0	327.0	417	423	419	359	308	436.0	339.0	182.0	109.0	63.7	0.0
66	33	2	2	A	1	0	32.4	174.0	226.0	301.0	339.0	416.0	451.0	518	522	527	372	329	247.0	171.0	87.5	61.7	28.3	0.0
67	34	1	1	A	1	0	51.2	174.0	214.0	335.0	658.0	729.0	1060.0	1130	1120	1090	915	891	613.0	676.0	491.0	329.0	139.0	13.8
68	34	1	2	B	1	0	0.0	146.0	314.0	580.0	1060.0	1220.0	1580.0	1390	1310	1270	1070	860	586.0	403.0	411.0	268.0	193.0	34.4
69	35	2	1	B	1	0	0.0	184.0	485.0	895.0	1050.0	1400.0	1660.0	1560	1420	1340	1100	1020	901.0	874.0	845.0	605.0	290.0	57.4
70	35	2	2	A	1	0	38.6	547.0	935.0	1080.0	1180.0	1220.0	1410.0	1580	1720	1790	1730	1690	1590.0	1700.0	1310.0	960.0	515.0	98.6
71	37	2	1	B	1	0	85.1	836.0	893.0	958.0	949.0	875.0	789.0	789	641	618	487	422	320.0	325.0	289.0	204.0	143.0	28.3
72	37	2	2	A	1	0	214.0	985.0	1230.0	1510.0	1730.0	1890.0	1760.0	1550	1350	1210	885	706	496.0	400.0	270.0	164.0	101.0	24.4
73	38	1	1	A	1	0	50.0	147.0	158.0	144.0	147.0	148.0	170.0	250	268	271	275	240	151.0	149.0	107.0	70.6	31.8	0.0
74	38	1	2	B	1	0	10.0	38.5	99.8	112.0	92.7	117.0	163.0	211	222	209	169	150	95.8	98.4	76.9	67.7	36.2	0.0
75	39	1	1	A	1	0	427.0	794.0	958.0	712.0	824.0	657.0	694.0	923	842	831	624	489	312.0	282.0	204.0	117.0	56.4	0.0
76	39	1	2	B	1	0	15.2	330.0	526.0	753.0	761.0	778.0	701.0	980	952	896	760	645	500.0	375.0	200.0	179.0	95.5	0.0
77	40	2	1	B	1	0	158.0	605.0	761.0	833.0	931.0	987.0	944.0	993	992	1030	869	905	949.0	726.0	707.0	567.0	408.0	139.0
78	40	2	2	A	1	0	421.0	729.0	805.0	826.0	708.0	769.0	784.0	807	922	840	788	672	585.0	658.0	567.0	434.0	331.0	123.0
79	41	2	1	B	1	0	11.8	285.0	385.0	581.0	789.0	895.0	927.0	1160	953	934	537	496	305.0	282.0	282.0	220.0	170.0	63.8
80	41	2	2	A	1	0	137.0	602.0	643.0	777.0	871.0	1010.0	1130.0	1070	874	761	602	455	345.0	348.0	285.0	235.0	153.0	41.1

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
81	42	1	1	A	1	0	20.8	171.0	833.0	1410.0	2270.0	2710.0	2830.0	2490	2130	1830	1180	1070	628.0	456.0	373.0	266.0	165.0	23.5
82	42	1	2	B	1	0	0.0	146.0	668.0	1350.0	1310.0	1360.0	1240.0	1160	1070	905	768	532	399.0	338.0	323.0	218.0	245.0	31.6
83	43	1	1	A	1	0	75.4	192.0	631.0	898.0	1290.0	1410.0	1700.0	2530	2980	2110	1740	1260	1200.0	1150.0	862.0	621.0	393.0	78.3
84	43	1	2	B	1	0	0.0	82.9	758.0	1410.0	2000.0	2080.0	2020.0	1730	1610	1540	1320	1020	1000.0	1390.0	1240.0	921.0	569.0	108.0
85	44	2	1	B	1	0	0.0	32.7	601.0	1150.0	1730.0	1820.0	2000.0	.	1610	1250	1080	865	641.0	523.0	392.0	229.0	254.0	25.8
86	44	2	2	A	1	0	114.0	884.0	1440.0	1840.0	1850.0	1710.0	1750.0	1640	1370	1130	1140	811	596.0	387.0	249.0	151.0	89.9	11.7
87	45	1	1	A	1	0	95.9	555.0	611.0	703.0	779.0	819.0	1160.0	1320	1440	1380	1210	1010	809.0	618.0	666.0	495.0	466.0	76.3
88	45	1	2	B	1	0	0.0	70.2	94.8	171.0	604.0	879.0	1660.0	1920	1860	1600	1570	1410	947.0	836.0	769.0	666.0	466.0	90.5
89	46	2	1	B	1	0	38.2	89.9	112.0	161.0	158.0	464.0	857.0	1090	1060	844	688	726	1670.0	856.0	601.0	341.0	260.0	35.9
90	46	2	2	A	1	0	966.0	1290.0	1320.0	1740.0	1570.0	1510.0	1570.0	1490	1370	1160	940	785	970.0	662.0	350.0	232.0	102.0	20.7
91	47	2	1	B	1	0	18.9	38.1	327.0	1000.0	1940.0	2160.0	2570.0	2050	1830	1510	1110	803	633.0	608.0	414.0	285.0	121.0	31.4
92	47	2	2	A	1	0	1210.0	2550.0	2620.0	2710.0	3150.0	3090.0	3000.0	2870	2490	2080	1640	1240	878.0	781.0	417.0	361.0	166.0	30.0
93	48	1	1	A	1	0	211.0	397.0	397.0	449.0	627.0	657.0	876.0	918	827	921	859	735	457.0	326.0	234.0	160.0	72.0	14.5
94	48	1	2	B	1	0	0.0	197.0	296.0	409.0	552.0	612.0	700.0	684	563	457	368	267	170.0	149.0	108.0	109.0	61.4	16.7
95	49	2	1	B	1	0	54.4	895.0	1030.0	1190.0	1360.0	1350.0	1400.0	1290	1190	985	819	588	467.0	433.0	376.0	253.0	187.0	23.2
96	49	2	2	A	1	0	600.0	1440.0	1550.0	1570.0	1660.0	1740.0	1720.0	1580	1370	1140	1090	846	751.0	528.0	272.0	226.0	83.3	12.6
97	50	1	1	A	1	0	96.8	345.0	462.0	509.0	624.0	557.0	532.0	530	485	432	356	261	246.0	186.0	148.0	109.0	47.2	0.0
98	50	1	2	B	1	0	0.0	227.0	790.0	836.0	1080.0	1360.0	1160.0	1010	906	739	695	464	303.0	226.0	165.0	136.0	45.7	0.0
99	51	2	1	B	1	0	13.2	306.0	498.0	639.0	729.0	628.0	622.0	525	503	499	428	457	261.0	162.0	95.3	89.8	39.1	0.0
100	51	2	2	A	1	0	133.0	498.0	760.0	830.0	851.0	971.0	886.0	748	702	656	497	467	297.0	215.0	160.0	109.0	53.8	0.0
101	52	1	1	A	1	0	108.0	491.0	603.0	683.0	806.0	868.0	806.0	737	667	585	452	361	251.0	190.0	127.0	119.0	44.5	10.2
102	52	1	2	B	1	0	0.0	156.0	511.0	1690.0	1470.0	1370.0	1390.0	1050	962	858	628	496	317.0	224.0	145.0	142.0	61.4	12.1
103	53	1	1	A	1	0	473.0	688.0	776.0	707.0	564.0	781.0	873.0	1100	1040	885	778	721	573.0	433.0	298.0	229.0	170.0	34.6
104	53	1	2	B	1	0	43.2	428.0	473.0	467.0	418.0	349.0	370.0	348	383	334	343	455	445.0	340.0	305.0	223.0	190.0	55.7
105	54	2	1	B	1	0	13.1	106.0	141.0	157.0	186.0	290.0	626.0	811	611	513	446	328	233.0	200.0	154.0	112.0	42.2	0.0
106	54	2	2	A	1	0	202.0	682.0	1040.0	1140.0	1260.0	1240.0	1370.0	1200	1020	801	584	488	303.0	214.0	109.0	77.4	29.9	0.0
107	55	2	1	B	1	0	0.0	13.8	19.6	25.7	72.5	136.0	351.0	827	1300	1070	881	817	694.0	542.0	471.0	384.0	200.0	33.0
108	55	2	2	A	1	0	171.0	380.0	483.0	541.0	696.0	760.0	1100.0	1040	1190	1050	871	768	677.0	556.0	541.0	419.0	217.0	38.8
109	56	1	1	A	1	0	932.0	918.0	836.0	862.0	714.0	579.0	597.0	524	477	449	320	248	170.0	178.0	119.0	98.6	51.0	12.5

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
110	56	1	2	B	1	0	41.2	747.0	1160.0	1280.0	1240.0	1200.0	1010.0	833	748	613	509	410	300.0	247.0	206.0	166.0	108.0	20.2
111	57	2	1	B	1	0	134.0	423.0	432.0	551.0	503.0	565.0	535.0	552	571	530	491	434	429.0	368.0	396.0	290.0	220.0	63.4
112	57	2	2	A	1	0	45.6	124.0	158.0	181.0	297.0	380.0	555.0	659	647	552	584	539	521.0	512.0	448.0	375.0	210.0	67.2
113	58	1	1	A	1	0	590.0	889.0	836.0	870.0	865.0	879.0	881.0	779	708	616	519	416	353.0	271.0	198.0	146.0	74.7	11.5
114	58	1	2	B	1	0	0.0	101.0	440.0	732.0	930.0	1040.0	1090.0	1020	865	751	543	392	307.0	284.0	163.0	133.0	75.1	18.2
115	59	2	1	B	1	0	15.2	42.5	46.2	50.8	59.1	54.4	82.5	170	186	276	3350	3700	3050.0	1790.0	1500.0	1100.0	869.0	164.0
116	59	2	2	A	1	0	124.0	319.0	445.0	435.0	521.0	576.0	789.0	731	736	678	784	1400	3330.0	2460.0	1740.0	1160.0	1050.0	231.0
117	60	1	1	A	1	0	55.0	259.0	415.0	492.0	763.0	785.0	995.0	859	847	790	582	460	441.0	360.0	226.0	191.0	98.1	20.5
118	60	1	2	B	1	0	0.0	75.7	161.0	386.0	586.0	962.0	1330.0	1300	1230	974	825	586	419.0	316.0	237.0	235.0	150.0	32.9
119	61	2	1	B	1	0	0.0	544.0	867.0	1000.0	1300.0	1250.0	1150.0	1140	1020	1000	820	634	441.0	337.0	397.0	492.0	302.0	87.9
120	61	2	2	A	1	0	163.0	572.0	1140.0	1480.0	1770.0	1420.0	1530.0	1400	1420	1390	1030	856	670.0	510.0	290.0	226.0	135.0	42.6
121	62	1	1	A	1	0	68.7	413.0	552.0	520.0	592.0	595.0	648.0	794	813	697	725	663	560.0	430.0	270.0	184.0	84.8	12.1
122	62	1	2	B	1	0	0.0	358.0	664.0	932.0	1020.0	1280.0	1250.0	1160	947	883	731	695	507.0	392.0	263.0	182.0	85.0	18.9
123	63	2	1	B	1	0	186.0	1470.0	1940.0	2050.0	2120.0	1820.0	1520.0	1170	1090	933	801	636	473.0	407.0	311.0	276.0	138.0	37.5
124	63	2	2	A	1	0	504.0	1520.0	1860.0	1710.0	2070.0	1910.0	1830.0	1720	1430	1300	1200	840	631.0	497.0	355.0	268.0	168.0	20.8
125	64	1	1	A	1	0	137.0	253.0	397.0	450.0	618.0	753.0	864.0	842	711	730	517	423	293.0	205.0	135.0	109.0	82.2	19.6
126	64	1	2	B	1	0	171.0	761.0	1080.0	1180.0	1100.0	1020.0	918.0	908	850	737	696	553	449.0	332.0	182.0	137.0	111.0	27.0
127	65	2	1	B	1	0	150.0	871.0	933.0	995.0	819.0	652.0	643.0	701	668	519	483	434	312.0	369.0	244.0	169.0	91.0	13.3
128	65	2	2	A	1	0	910.0	2190.0	2180.0	2410.0	2280.0	1990.0	1900.0	1610	1430	1170	956	839	724.0	566.0	317.0	209.0	83.4	13.6
129	66	1	1	A	1	0	79.8	289.0	651.0	910.0	975.0	890.0	1080.0	806	791	741	637	508	505.0	406.0	313.0	214.0	124.0	31.5
130	66	1	2	B	1	0	18.8	454.0	614.0	683.0	772.0	756.0	861.0	877	968	845	747	623	542.0	553.0	368.0	273.0	187.0	21.3
131	67	2	1	B	1	0	0.0	18.1	77.8	188.0	351.0	429.0	695.0	837	934	1330	616	706	565.0	400.0	327.0	249.0	197.0	44.9
132	67	2	2	A	1	0	53.4	168.0	179.0	228.0	288.0	299.0	349.0	525	678	828	1080	1280	1070.0	679.0	465.0	312.0	244.0	59.0
133	68	1	1	A	1	0	251.0	314.0	297.0	313.0	306.0	336.0	488.0	528	448	427	411	387	324.0	216.0	97.1	59.1	32.2	0.0
134	68	1	2	B	1	0	38.6	165.0	208.0	307.0	405.0	436.0	595.0	638	573	505	426	358	242.0	172.0	97.8	73.6	37.3	10.1
135	69	1	1	A	1	0	129.0	478.0	565.0	552.0	649.0	645.0	847.0	1040	1080	904	728	529	370.0	286.0	191.0	154.0	58.0	0.0
136	69	1	2	B	1	0	96.0	253.0	299.0	374.0	414.0	438.0	552.0	597	612	549	467	397	385.0	398.0	240.0	160.0	67.3	0.0
137	70	2	1	B	1	0	114.0	530.0	699.0	851.0	986.0	973.0	1020.0	790	671	514	441	365	231.0	152.0	147.0	118.0	60.6	0.0
138	70	2	2	A	1	0	466.0	1300.0	1380.0	1340.0	1260.0	1220.0	1240.0	1020	1270	1090	947	838	551.0	359.0	214.0	157.0	62.2	0.0

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
139	71	1	1	A	1	0	127.0	656.0	891.0	830.0	986.0	863.0	759.0	626	545	491	461	410	404.0	364.0	276.0	190.0	149.0	34.3
140	71	1	2	B	1	0	0.0	15.8	38.3	102.0	308.0	544.0	830.0	805	837	702	591	517	457.0	462.0	425.0	311.0	218.0	48.5
141	72	2	1	B	1	0	0.0	14.1	49.8	83.5	139.0	184.0	217.0	280	320	303	280	244	167.0	144.0	122.0	106.0	140.0	26.1
142	72	2	2	A	1	0	20.1	207.0	285.0	317.0	346.0	395.0	461.0	545	521	483	439	309	228.0	157.0	125.0	91.1	104.0	14.4
143	73	2	1	B	1	0	15.9	114.0	499.0	1040.0	1490.0	1360.0	1500.0	1200	1130	833	808	497	388.0	277.0	207.0	150.0	110.0	21.4
144	73	2	2	A	1	0	141.0	354.0	373.0	840.0	1220.0	1220.0	1270.0	1390	1290	1090	881	801	798.0	690.0	464.0	307.0	175.0	30.3
145	74	1	1	A	1	0	387.0	612.0	677.0	633.0	706.0	687.0	619.0	536	456	432	341	290	198.0	131.0	76.1	44.3	18.8	0.0
146	74	1	2	B	1	0	27.2	707.0	835.0	945.0	1060.0	1090.0	1020.0	924	756	621	508	374	231.0	202.0	143.0	103.0	45.5	0.0
147	75	2	1	B	1	0	26.2	471.0	759.0	817.0	843.0	774.0	577.0	517	419	364	307	248	208.0	155.0	106.0	87.5	45.8	0.0
148	75	2	2	A	1	0	185.0	695.0	807.0	770.0	732.0	744.0	703.0	522	568	439	435	319	302.0	238.0	135.0	89.5	62.0	12.6
149	76	1	1	A	1	0	78.8	166.0	182.0	239.0	404.0	444.0	725.0	800	863	931	994	779	674.0	526.0	450.0	306.0	184.0	44.8
150	76	1	2	B	1	0	11.8	125.0	385.0	712.0	885.0	990.0	1060.0	1010	921	712	519	399	249.0	213.0	142.0	102.0	47.3	0.0
151	77	1	1	A	1	0	249.0	689.0	742.0	778.0	881.0	762.0	806.0	895	722	667	508	409	270.0	197.0	131.0	77.8	37.8	0.0
152	77	1	2	B	1	0	103.0	669.0	1180.0	1170.0	1320.0	1220.0	1240.0	1480	1350	1250	1100	880	756.0	645.0	346.0	267.0	116.0	11.6
153	78	2	1	B	1	0	178.0	382.0	482.0	547.0	605.0	637.0	745.0	594	554	517	478	475	431.0	308.0	194.0	157.0	74.5	0.0
154	78	2	2	A	1	0	368.0	571.0	681.0	719.0	865.0	868.0	888.0	839	722	623	535	495	356.0	248.0	191.0	138.0	87.4	11.8
155	79	1	1	A	1	0	138.0	415.0	525.0	606.0	659.0	711.0	636.0	544	515	434	420	361	223.0	179.0	78.3	81.4	38.2	0.0
156	79	1	2	B	1	0	17.8	124.0	284.0	389.0	467.0	520.0	571.0	522	496	437	404	354	230.0	215.0	103.0	84.1	45.6	12.0
157	80	2	1	B	1	0	122.0	630.0	892.0	970.0	928.0	916.0	917.0	816	794	618	545	450	376.0	352.0	308.0	345.0	317.0	71.7
158	80	2	2	A	1	0	399.0	1150.0	1220.0	1290.0	1260.0	1190.0	1080.0	823	887	821	718	506	378.0	329.0	273.0	210.0	205.0	38.1

90379 Fasting REVIEWER-CALCULATED PHARMACOKINETIC DATASET

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
1	1	1	2	2	1	16731.45	17418.60	1320	10.00	8.13	0.08528
2	1	2	2	1	1	12180.55	12504.02	1660	5.50	7.79	0.08904
3	2	1	1	1	1	10446.90	10844.19	975	3.00	10.43	0.06645
4	2	2	1	2	1	10217.80	10415.18	1230	3.50	6.42	0.10791
5	3	1	2	2	1	9461.25	9540.43	789	6.00	4.99	0.13893

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
6	3	2	2	1	1	7550.93	7652.78	884	5.50	5.79	0.11978
7	4	1	1	1	1	12860.70	13205.12	1740	3.00	4.43	0.15649
8	4	2	1	2	1	10784.70	11172.28	1440	2.50	4.85	0.14294
9	5	1	1	1	1	17970.60	18393.42	1460	4.50	7.65	0.09058
10	5	2	1	2	1	22432.90	24416.37	1420	4.50	14.80	0.04684
11	6	1	2	2	1	26835.40	28296.14	1530	10.00	10.02	0.06914
12	6	2	2	1	1	20420.78	22701.79	1150	5.00	14.12	0.04910
13	7	1	2	2	1	17784.40	18004.89	2100	3.50	6.14	0.11293
14	7	2	2	1	1	19507.75	19606.88	2530	4.00	4.98	0.13921
15	8	1	1	1	1	6944.55	7494.56	550	6.00	18.60	0.03727
16	8	2	1	2	1	11235.20	11819.15	559	6.00	17.52	0.03956
17	9	1	2	2	1	31597.10	31789.98	5560	3.00	5.10	0.13584
18	9	2	2	1	1	27332.60	27619.28	2870	3.00	6.39	0.10848
19	10	1	1	1	1	12721.30	13129.00	1660	4.50	4.70	0.14741
20	10	2	1	2	1	13944.00	14072.17	2130	3.50	5.52	0.12562
21	11	1	2	2	1	15867.70	16592.91	1570	4.50	10.43	0.06646
22	11	2	2	1	1	12539.80	12912.04	1350	4.50	8.14	0.08516
23	12	1	1	1	1	13457.70	14068.43	1570	3.50	4.96	0.13983
24	12	2	1	2	1	13945.80	14032.42	2040	5.00	5.09	0.13622
25	13	1	1	1	1	7514.40	8047.53	898	3.00	6.08	0.11404
26	13	2	1	2	1	4940.15	6151.65	457	4.50	9.82	0.07057
27	14	1	2	2	1	2806.80	2982.02	382	5.00	6.04	0.11471
28	14	2	2	1	1	2947.00	3258.35	318	8.00	5.91	0.11723
29	15	1	1	1	1	9205.40	9704.31	984	7.00	5.22	0.13289
30	15	2	1	2	1	6370.60	6941.13	680	5.50	5.88	0.11779
31	16	1	2	2	1	6540.85	6826.04	712	4.00	4.74	0.14622
32	16	2	2	1	1	4211.73	5124.43	272	5.00	7.29	0.09510
33	17	1	2	2	1	5592.63	5964.21	548	5.50	4.67	0.14855
34	17	2	2	1	1	4427.30	4816.29	501	5.00	5.69	0.12185

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
35	18	1	1	1	1	8825.35	9288.06	731	3.50	11.66	0.05943
36	18	2	1	2	1	7969.65	9698.79	335	15.00	32.31	0.02146
37	19	1	1	1	1	3845.10	4174.54	381	6.00	6.36	0.10897
38	19	2	1	2	1	5237.35	5454.00	395	5.00	12.73	0.05447
39	20	1	2	2	1	10727.00	10841.75	890	5.00	5.37	0.12898
40	20	2	2	1	1	9173.15	9280.58	710	4.50	5.44	0.12753
41	21	1	2	2	1	29939.60	31299.21	1750	5.50	8.73	0.07943
42	21	2	2	1	1	29098.60	33331.60	1420	5.50	17.26	0.04016
43	22	1	1	1	1	13800.90	14084.23	1450	4.50	7.73	0.08965
44	22	2	1	2	1	14832.58	15138.08	2770	4.50	6.42	0.10802
45	23	1	2	2	1	15631.55	15919.17	1520	5.00	6.71	0.10326
46	23	2	2	1	1	11537.00	11708.07	1340	5.50	6.11	0.11340
47	24	1	1	1	1	14687.45	15833.11	1280	3.00	30.90	0.02243
48	24	2	1	2	1	11372.28	11623.08	985	7.00	6.61	0.10486
49	25	1	1	1	1	11004.35	11111.70	945	3.00	5.95	0.11644
50	25	2	1	2	1	10354.95	10434.82	844	5.50	5.22	0.13271
51	26	1	2	2	1	17038.30	17221.67	2040	4.50	5.78	0.11998
52	26	2	2	1	1	9709.50	9988.56	791	5.00	9.12	0.07597
53	27	1	2	2	1	13012.50	13084.25	1340	5.50	4.44	0.15610
54	27	2	2	1	1	8970.55	9674.13	1050	5.00	5.83	0.11882
55	28	1	1	1	1	11595.80	11808.25	818	12.00	5.10	0.13603
56	28	2	1	2	1	9261.75	9676.67	661	5.50	7.37	0.09399
57	29	1	1	1	1	3785.95	3913.81	598	3.00	5.21	0.13295
58	29	2	1	2	1	2917.78	3033.06	408	6.00	4.76	0.14572
59	30	1	2	2	1	8079.35	8446.93	519	3.50	7.94	0.08733
60	30	2	2	1	1	6244.30	7031.49	431	3.50	9.98	0.06949
61	31	1	1	1	1	7187.95	7687.10	804	8.00	4.84	0.14324
62	31	2	1	2	1	7936.05	8020.24	778	5.00	5.26	0.13185
63	32	1	2	2	1	17548.05	17670.18	1890	4.00	4.76	0.14575

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
64	32	2	2	1	1	17240.20	17491.18	2010	3.00	6.64	0.10439
65	33	1	2	2	1	4356.70	4552.21	527	6.00	4.79	0.14475
66	33	2	2	1	1	5221.35	5688.59	436	10.00	5.08	0.13633
67	34	1	1	1	1	13077.00	13180.53	1130	5.00	5.20	0.13330
68	34	2	1	2	1	13710.90	14220.12	1580	4.50	10.26	0.06755
69	35	1	2	2	1	31525.45	32507.93	1790	6.00	6.91	0.10036
70	35	2	2	1	1	20206.90	20798.05	1660	4.50	7.14	0.09710
71	37	1	2	2	1	13909.65	14121.39	1890	4.00	6.02	0.11523
72	37	2	2	1	1	9936.90	10332.98	958	3.00	9.70	0.07145
73	38	1	1	1	1	3049.60	3294.15	275	7.00	5.33	0.13004
74	38	2	1	2	1	2179.93	2620.15	222	5.50	8.43	0.08223
75	39	1	1	1	1	8444.95	8856.39	958	2.50	5.06	0.13708
76	39	2	1	2	1	9017.20	9915.41	980	5.00	6.52	0.10632
77	40	1	2	2	1	16390.25	18489.09	922	5.50	11.83	0.05860
78	40	2	2	1	1	19722.75	22448.66	1030	6.00	13.59	0.05099
79	41	1	2	2	1	10727.35	11327.61	1130	4.50	10.12	0.06847
80	41	2	2	1	1	10115.85	11510.53	1160	5.00	15.15	0.04575
81	42	1	1	1	1	17981.05	18252.65	2830	4.50	8.01	0.08653
82	42	2	1	2	1	12420.85	13458.22	1360	4.00	22.75	0.03046
83	43	1	1	1	1	25813.70	26686.96	2980	5.50	7.73	0.08966
84	43	2	1	2	1	28979.68	30378.36	2080	4.00	8.98	0.07722
85	44	1	2	2	1	14246.30	14342.61	1850	3.50	5.71	0.12148
86	44	2	2	1	1	15934.33	16353.60	2000	4.50	11.26	0.06153
87	45	1	1	1	1	19728.45	22410.52	1440	5.50	24.37	0.02845
88	45	2	1	2	1	22557.05	24371.64	1920	5.00	13.90	0.04987
89	46	1	2	2	1	16937.20	17073.31	1740	3.00	4.56	0.15209
90	46	2	2	1	1	15839.53	16195.69	1670	10.00	6.88	0.10080
91	47	1	2	2	1	26405.50	26651.08	3150	3.50	5.67	0.12216
92	47	2	2	1	1	16020.88	16254.14	2570	4.50	5.15	0.13461

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
93	48	1	1	1	1	9422.50	9536.90	921	6.00	5.47	0.12675
94	48	2	1	2	1	5346.80	5586.15	700	4.50	9.93	0.06977
95	49	1	2	2	1	15969.30	16054.77	1740	4.00	4.70	0.14741
96	49	2	2	1	1	13675.60	13993.18	1400	4.50	9.49	0.07305
97	50	1	1	1	1	5309.65	5716.18	624	3.53	5.97	0.11610
98	50	2	1	2	1	8101.60	8445.58	1360	4.00	5.22	0.13286
99	51	1	2	2	1	7333.40	7794.12	971	4.00	5.94	0.11677
100	51	2	2	1	1	5536.75	5884.92	729	3.50	6.17	0.11230
101	52	1	1	1	1	6848.70	6935.61	868	4.00	5.91	0.11736
102	52	2	1	2	1	9247.20	9364.85	1690	3.00	6.74	0.10285
103	53	1	1	1	1	12323.35	12781.45	1100	5.00	9.18	0.07553
104	53	2	1	2	1	8746.90	9843.53	473	2.53	13.65	0.05079
105	54	1	2	2	1	8671.25	8859.17	1370	4.50	4.36	0.15911
106	54	2	2	1	1	4884.95	5206.06	811	5.00	5.27	0.13142
107	55	1	2	2	1	14609.80	15079.77	1190	5.50	8.40	0.08256
108	55	2	2	1	1	12167.25	12556.75	1300	5.50	8.18	0.08472
109	56	1	1	1	1	7063.45	7186.89	932	1.00	6.85	0.10126
110	56	2	1	2	1	9596.40	9887.02	1280	3.00	9.97	0.06951
111	57	1	2	2	1	11030.30	11919.89	659	5.00	9.18	0.07554
112	57	2	2	1	1	10476.65	11784.95	571	5.50	14.30	0.04846
113	58	1	1	1	1	9146.55	9253.65	889	2.00	6.46	0.10738
114	58	2	1	2	1	8025.10	8197.82	1090	4.50	6.58	0.10537
115	59	1	2	2	1	39958.25	43246.95	3330	10.00	9.87	0.07024
116	59	2	2	1	1	38308.58	40974.08	3700	8.00	11.27	0.06153
117	60	1	1	1	1	9017.15	9213.94	995	4.50	6.65	0.10417
118	60	2	1	2	1	10412.68	10975.38	1330	4.50	11.86	0.05847
119	61	1	2	2	1	15001.10	15404.71	1770	3.50	6.57	0.10555
120	61	2	2	1	1	15167.40	23557.34	1300	3.50	66.16	0.01048
121	62	1	1	1	1	9546.50	9636.84	813	5.50	5.17	0.13394

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
122	62	2	1	2	1	10811.15	10960.05	1280	4.00	5.46	0.12693
123	63	1	2	2	1	17756.30	17989.39	2070	3.50	7.77	0.08924
124	63	2	2	1	1	15203.75	15626.44	2120	3.50	7.81	0.08872
125	64	1	1	1	1	7194.65	7465.33	864	4.50	9.57	0.07241
126	64	2	1	2	1	10399.50	10716.54	1180	3.00	8.14	0.08516
127	65	1	2	2	1	18131.20	18217.79	2410	3.00	4.41	0.15706
128	65	2	2	1	1	8969.80	9084.84	995	3.00	6.00	0.11561
129	66	1	1	1	1	10534.80	10848.77	1080	4.50	6.91	0.10033
130	66	2	1	2	1	12049.85	12291.84	968	5.50	7.87	0.08802
131	67	1	2	2	1	14259.90	14959.67	1280	8.00	8.22	0.08431
132	67	2	2	1	1	10715.88	11470.94	1330	6.00	11.66	0.05947
133	68	1	1	1	1	4998.10	5209.05	528	5.00	4.54	0.15264
134	68	2	1	2	1	5020.00	5102.14	638	5.00	5.64	0.12297
135	69	1	1	1	1	8271.00	8713.34	1080	5.50	5.29	0.13112
136	69	2	1	2	1	6809.90	7269.08	612	5.50	4.73	0.14657
137	70	1	2	2	1	12362.10	12796.00	1380	2.50	4.84	0.14335
138	70	2	2	1	1	6876.30	7631.18	1020	4.50	8.63	0.08028
139	71	1	1	1	1	9761.05	10219.33	986	3.52	9.26	0.07485
140	71	2	1	2	1	10633.50	11371.01	837	5.50	10.54	0.06576
141	72	1	2	2	1	5530.95	5954.81	545	5.00	20.40	0.03397
142	72	2	2	1	1	4474.08	48297.30	320	5.50	1163.83	0.00060
143	73	1	2	2	1	14959.30	15225.17	1390	5.00	6.08	0.11397
144	73	2	2	1	1	10272.05	10551.13	1500	4.50	9.04	0.07668
145	74	1	1	1	1	5310.55	5427.17	706	3.50	4.30	0.16121
146	74	2	1	2	1	7403.20	7769.23	1090	4.00	5.58	0.12431
147	75	1	2	2	1	7012.35	7128.57	807	2.50	6.39	0.10841
148	75	2	2	1	1	5337.10	5799.32	843	3.50	7.00	0.09909
149	76	1	1	1	1	12207.35	12701.11	994	7.00	7.64	0.09073
150	76	2	1	2	1	6795.95	7176.15	1060	4.50	5.57	0.12441

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
151	77	1	1	1	1	7069.50	7342.04	895	5.00	5.00	0.13870
152	77	2	1	2	1	14919.85	15004.11	1480	5.00	5.04	0.13766
153	78	1	2	2	1	8715.40	8850.23	888	4.50	7.92	0.08752
154	78	2	2	1	1	7268.75	7917.34	745	4.50	6.03	0.11487
155	79	1	1	1	1	5443.55	5772.09	711	4.00	5.96	0.11627
156	79	2	1	2	1	5165.40	5264.71	571	4.50	5.74	0.12083
157	80	1	2	2	1	12645.35	13610.11	1290	3.00	17.55	0.03949
158	80	2	2	1	1	12786.20	26180.74	970	3.00	129.49	0.00535

4.7.2 Fasting Study Output

Fasting STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	79	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Number of Observations Read	158
Number of Observations Used	158

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	80	44.37904203	0.55473803	16.78	<.0001
Error	77	2.54621738	0.03306776		
Corrected Total	157	46.92525941			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.945739	1.966251	0.181845	9.248330

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	2.56873934	2.56873934	77.68	<.0001
SUB(SEQ)	77	40.92916527	0.53154760	16.07	<.0001
PER	1	0.46467334	0.46467334	14.05	0.0003
TRT	1	0.41646409	0.41646409	12.59	0.0007

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	2.56873934	2.56873934	77.68	<.0001
SUB(SEQ)	77	40.92916527	0.53154760	16.07	<.0001
PER	1	0.45352957	0.45352957	13.72	0.0004
TRT	1	0.41646409	0.41646409	12.59	0.0007

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	2.56873934	2.56873934	4.83	0.0309

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.10268926	0.02893601	3.55	0.0007

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	80	41.94694607	0.52433683	17.37	<.0001
Error	77	2.32456831	0.03018920		
Corrected Total	157	44.27151438			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.947493	1.871094	0.173750	9.286034

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	2.60224569	2.60224569	86.20	<.0001
SUB(SEQ)	77	38.63903446	0.50180564	16.62	<.0001
PER	1	0.39928706	0.39928706	13.23	0.0005
TRT	1	0.30637886	0.30637886	10.15	0.0021

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	2.60224569	2.60224569	86.20	<.0001
SUB(SEQ)	77	38.63903446	0.50180564	16.62	<.0001
PER	1	0.39041816	0.39041816	12.93	0.0006
TRT	1	0.30637886	0.30637886	10.15	0.0021

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	2.60224569	2.60224569	5.19	0.0255

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.08807764	0.02764789	3.19	0.0021

Fasting STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	80	44.57862998	0.55723287	8.75	<.0001
Error	77	4.90330337	0.06367926		
Corrected Total	157	49.48193335			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.900907	3.621988	0.252348	6.967099

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	1.70389197	1.70389197	26.76	<.0001
SUB(SEQ)	77	42.08620013	0.54657403	8.58	<.0001
PER	1	0.37621665	0.37621665	5.91	0.0174
TRT	1	0.41232123	0.41232123	6.47	0.0129

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.70389197	1.70389197	26.76	<.0001
SUB(SEQ)	77	42.08620013	0.54657403	8.58	<.0001
PER	1	0.36625221	0.36625221	5.75	0.0189
TRT	1	0.41232123	0.41232123	6.47	0.0129

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.70389197	1.70389197	3.12	0.0814

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.10217722	0.04015460	2.54	0.0129

90379 Fasting FIRM TO REVIEWER RATIO

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	2	2	1	1	16731.45	17418.60	1320	A	16731.45	17216.32	1320	1.00000	0.98839	1
2	1	2	1	1	2	12180.55	12504.02	1660	B	12180.55	12414.17	1660	1.00000	0.99281	1
3	2	1	1	1	1	10446.90	10844.19	975	A	10446.90	10697.30	975	1.00000	0.98645	1
4	2	1	2	1	2	10217.80	10415.18	1230	B	10226.02	10398.34	1230	1.00080	0.99838	1
5	3	2	2	1	1	9461.25	9540.43	789	A	9461.25	9531.75	789	1.00000	0.99909	1
6	3	2	1	1	2	7550.93	7652.78	884	B	7550.93	7638.61	884	1.00000	0.99815	1
7	4	1	1	1	1	12860.70	13205.12	1740	A	12860.70	13230.44	1740	1.00000	1.00192	1
8	4	1	2	1	2	10784.70	11172.28	1440	B	10784.70	11201.56	1440	1.00000	1.00262	1
9	5	1	1	1	1	17970.60	18393.42	1460	A	17970.60	18223.97	1460	1.00000	0.99079	1
10	5	1	2	1	2	22432.90	24416.37	1420	B	22432.90	23208.88	1420	1.00000	0.95055	1
11	6	2	2	1	1	26835.40	28296.14	1530	A	26835.40	27687.77	1530	1.00000	0.97850	1
12	6	2	1	1	2	20420.78	22701.79	1150	B	20420.78	21504.58	1150	1.00000	0.94726	1
13	7	2	2	1	1	17784.40	18004.89	2100	A	17784.40	17971.42	2100	1.00000	0.99814	1
14	7	2	1	1	2	19507.75	19606.88	2530	B	19507.75	19594.26	2530	1.00000	0.99936	1
15	8	1	1	1	1	6944.55	7494.56	550	A	6944.55	7099.89	550	1.00000	0.94734	1
16	8	1	2	1	2	11235.20	11819.15	559	B	11235.20	11369.37	559	1.00000	0.96195	1
17	9	2	2	1	1	31597.10	31789.98	5560	A	31597.10	31772.84	5560	1.00000	0.99946	1
18	9	2	1	1	2	27332.60	27619.28	2870	B	27332.60	27526.00	2870	1.00000	0.99662	1
19	10	1	1	1	1	12721.30	13129.00	1660	A	12721.30	13126.94	1660	1.00000	0.99984	1
20	10	1	2	1	2	13944.00	14072.17	2130	B	13948.30	14070.81	2130	1.00031	0.99990	1
21	11	2	2	1	1	15867.70	16592.91	1570	A	15867.70	16273.17	1570	1.00000	0.98073	1
22	11	2	1	1	2	12539.80	12912.04	1350	B	12539.80	12780.02	1350	1.00000	0.98978	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
23	12	1	1	1	1	13457.70	14068.43	1570	A	13457.70	14079.43	1570	1.00000	1.00078	1
24	12	1	2	1	2	13945.80	14032.42	2040	B	13945.80	14021.85	2040	1.00000	0.99925	1
25	13	1	1	1	1	7514.40	8047.53	898	A	7514.40	8172.44	898	1.00000	1.01552	1
26	13	1	2	1	2	4940.15	6151.65	457	B	4940.15	6491.59	457	1.00000	1.05526	1
27	14	2	2	1	1	2806.80	2982.02	382	A	2806.80	3000.10	382	1.00000	1.00606	1
28	14	2	1	1	2	2947.00	3258.35	318	B	2947.00	3263.27	318	1.00000	1.00151	1
29	15	1	1	1	1	9205.40	9704.31	984	A	9205.40	9718.51	984	1.00000	1.00146	1
30	15	1	2	1	2	6370.60	6941.13	680	B	6370.60	6994.27	680	1.00000	1.00766	1
31	16	2	2	1	1	6540.85	6826.04	712	A	6540.85	6820.99	712	1.00000	0.99926	1
32	16	2	1	1	2	4211.73	5124.43	272	B	4211.73	5106.23	272	1.00000	0.99645	1
33	17	2	2	1	1	5592.63	5964.21	548	A	5592.63	5984.97	548	1.00000	1.00348	1
34	17	2	1	1	2	4427.30	4816.29	501	B	4427.30	4883.28	501	1.00000	1.01391	1
35	18	1	1	1	1	8825.35	9288.06	731	A	8841.81	9062.05	731	1.00187	0.97567	1
36	18	1	2	1	2	7969.65	9698.79	335	B	7974.00	8269.89	335	1.00055	0.85267	1
37	19	1	1	1	1	3845.10	4174.54	381	A	3845.10	4188.84	381	1.00000	1.00342	1
38	19	1	2	1	2	5237.35	5454.00	395	B	5280.40	5361.48	395	1.00822	0.98304	1
39	20	2	2	1	1	10727.00	10841.75	890	A	10729.18	10821.93	890	1.00020	0.99817	1
40	20	2	1	1	2	9173.15	9280.58	710	B	9173.15	9266.16	710	1.00000	0.99845	1
41	21	2	2	1	1	29939.60	31299.21	1750	A	29945.41	30815.93	1750	1.00019	0.98456	1
42	21	2	1	1	2	29098.60	33331.60	1420	B	29098.60	30776.78	1420	1.00000	0.92335	1
43	22	1	1	1	1	13800.90	14084.23	1450	A	13800.90	14003.91	1450	1.00000	0.99430	1
44	22	1	2	1	2	14832.58	15138.08	2770	B	14832.58	15143.73	2770	1.00000	1.00037	1
45	23	2	2	1	1	15631.55	15919.17	1520	A	15633.23	15860.11	1520	1.00011	0.99629	1
46	23	2	1	1	2	11537.00	11708.07	1340	B	11553.15	11695.32	1340	1.00140	0.99891	1
47	24	1	1	1	1	14687.45	15833.11	1280	A	14678.95	14840.37	1280	0.99942	0.93730	1
48	24	1	2	1	2	11372.28	11623.08	985	B	11365.13	11576.09	985	0.99937	0.99596	1
49	25	1	1	1	1	11004.35	11111.70	945	A	11004.35	11084.27	945	1.00000	0.99753	1
50	25	1	2	1	2	10354.95	10434.82	844	B	10354.95	10413.70	844	1.00000	0.99798	1
51	26	2	2	1	1	17038.30	17221.67	2040	A	17039.55	17190.86	2040	1.00007	0.99821	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
52	26	2	1	1	2	9709.50	9988.56	791	B	9711.06	9872.11	791	1.00016	0.98834	1
53	27	2	2	1	1	13012.50	13084.25	1340	A	13013.02	13077.30	1340	1.00004	0.99947	1
54	27	2	1	1	2	8970.55	9674.13	1050	B	8970.55	9698.82	1050	1.00000	1.00255	1
55	28	1	1	1	1	11595.80	11808.25	818	A	11595.80	11826.82	818	1.00000	1.00157	1
56	28	1	2	1	2	9261.75	9676.67	661	B	9276.08	9699.83	661	1.00155	1.00239	1
57	29	1	1	1	1	3785.95	3913.81	598	A	3785.95	3936.41	598	1.00000	1.00577	1
58	29	1	2	1	2	2917.78	3033.06	408	B	2917.78	3051.57	408	1.00000	1.00610	1
59	30	2	2	1	1	8079.35	8446.93	519	A	8079.35	8385.52	519	1.00000	0.99273	1
60	30	2	1	1	2	6244.30	7031.49	431	B	6244.30	7102.29	431	1.00000	1.01007	1
61	31	1	1	1	1	7187.95	7687.10	804	A	7187.95	7721.56	804	1.00000	1.00448	1
62	31	1	2	1	2	7936.05	8020.24	778	B	7936.05	8014.81	778	1.00000	0.99932	1
63	32	2	2	1	1	17548.05	17670.18	1890	A	17548.05	17662.57	1890	1.00000	0.99957	1
64	32	2	1	1	2	17240.20	17491.18	2010	B	17240.20	17431.97	2010	1.00000	0.99661	1
65	33	2	2	1	1	4356.70	4552.21	527	A	4356.70	4581.20	527	1.00000	1.00637	1
66	33	2	1	1	2	5221.35	5688.59	436	B	5221.35	5786.20	436	1.00000	1.01716	1
67	34	1	1	1	1	13077.00	13180.53	1130	A	13102.47	13181.27	1130	1.00195	1.00006	1
68	34	1	2	1	2	13710.90	14220.12	1580	B	13724.09	14016.25	1580	1.00096	0.98566	1
69	35	2	2	1	1	31525.45	32507.93	1790	A	31714.64	32512.37	1790	1.00600	1.00014	1
70	35	2	1	1	2	20206.90	20798.05	1660	B	20206.90	20643.62	1660	1.00000	0.99257	1
71	37	2	2	1	1	13909.65	14121.39	1890	A	13914.88	14142.65	1890	1.00038	1.00151	1
72	37	2	1	1	2	9936.90	10332.98	958	B	9936.90	10186.58	958	1.00000	0.98583	1
73	38	1	1	1	1	3049.60	3294.15	275	A	3049.60	3285.95	275	1.00000	0.99751	1
74	38	1	2	1	2	2179.93	2620.15	222	B	2179.93	2597.64	222	1.00000	0.99141	1
75	39	1	1	1	1	8444.95	8856.39	958	A	8444.95	8848.33	958	1.00000	0.99909	1
76	39	1	2	1	2	9017.20	9915.41	980	B	9017.20	10136.02	980	1.00000	1.02225	1
77	40	2	2	1	1	16390.25	18489.09	922	A	16405.38	18124.36	922	1.00092	0.98027	1
78	40	2	1	1	2	19722.75	22448.66	1030	B	19722.75	21465.35	1030	1.00000	0.95620	1
79	41	2	2	1	1	10727.35	11327.61	1130	A	10727.35	11143.87	1130	1.00000	0.98378	1
80	41	2	1	1	2	10115.85	11510.53	1160	B	10115.85	11019.35	1160	1.00000	0.95733	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
81	42	1	1	1	1	17981.05	18252.65	2830	A	17981.05	18150.42	2830	1.00000	0.99440	1
82	42	1	2	1	2	12420.85	13458.22	1360	B	12420.85	12692.44	1360	1.00000	0.94310	1
83	43	1	1	1	1	25813.70	26686.96	2980	A	25813.70	26478.31	2980	1.00000	0.99218	1
84	43	1	2	1	2	28979.68	30378.36	2080	B	28979.68	29866.04	2080	1.00000	0.98314	1
85	44	2	2	1	1	14246.30	14342.61	1850	A	14246.30	14326.40	1850	1.00000	0.99887	1
86	44	2	1	1	2	15934.33	16353.60	2000	B	15924.92	16121.57	2000	0.99941	0.98581	1
87	45	1	1	1	1	19728.45	22410.52	1440	A	19728.45	20418.42	1440	1.00000	0.91111	1
88	45	1	2	1	2	22557.05	24371.64	1920	B	22557.05	23347.06	1920	1.00000	0.95796	1
89	46	2	2	1	1	16937.20	17073.31	1740	A	16937.20	17091.61	1740	1.00000	1.00107	1
90	46	2	1	1	2	15839.53	16195.69	1670	B	15839.53	16114.06	1670	1.00000	0.99496	1
91	47	2	2	1	1	26405.50	26651.08	3150	A	26405.50	26621.59	3150	1.00000	0.99889	1
92	47	2	1	1	2	16020.88	16254.14	2570	B	16020.88	16280.18	2570	1.00000	1.00160	1
93	48	1	1	1	1	9422.50	9536.90	921	A	9422.50	9531.19	921	1.00000	0.99940	1
94	48	1	2	1	2	5346.80	5586.15	700	B	5346.80	5506.11	700	1.00000	0.98567	1
95	49	2	2	1	1	15969.30	16054.77	1740	A	15969.30	16048.07	1740	1.00000	0.99958	1
96	49	2	1	1	2	13675.60	13993.18	1400	B	13675.60	13842.97	1400	1.00000	0.98927	1
97	50	1	1	1	1	5309.65	5716.18	624	A	5305.81	5672.36	624	0.99928	0.99233	1
98	50	1	2	1	2	8101.60	8445.58	1360	B	8101.60	8409.89	1360	1.00000	0.99577	1
99	51	2	2	1	1	7333.40	7794.12	971	A	7333.40	7779.46	971	1.00000	0.99812	1
100	51	2	1	1	2	5536.75	5884.92	729	B	5536.75	5910.39	729	1.00000	1.00433	1
101	52	1	1	1	1	6848.70	6935.61	868	A	6844.08	6919.90	868	0.99933	0.99773	1
102	52	1	2	1	2	9247.20	9364.85	1690	B	9247.20	9335.78	1690	1.00000	0.99690	1
103	53	1	1	1	1	12323.35	12781.45	1100	A	12322.73	12640.32	1100	0.99995	0.98896	1
104	53	1	2	1	2	8746.90	9843.53	473	B	8746.25	9436.77	473	0.99993	0.95868	1
105	54	2	2	1	1	8671.25	8859.17	1370	A	8671.25	8876.28	1370	1.00000	1.00193	1
106	54	2	1	1	2	4884.95	5206.06	811	B	4883.84	5171.84	811	0.99977	0.99343	1
107	55	2	2	1	1	14609.80	15079.77	1190	A	14609.80	14899.78	1190	1.00000	0.98806	1
108	55	2	1	1	2	12167.25	12556.75	1300	B	12163.38	12401.96	1300	0.99968	0.98767	1
109	56	1	1	1	1	7063.45	7186.89	932	A	7064.17	7172.76	932	1.00010	0.99803	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
110	56	1	2	1	2	9596.40	9887.02	1280	B	9596.40	9764.37	1280	1.00000	0.98759	1
111	57	2	2	1	1	11030.30	11919.89	659	A	11030.30	11734.45	659	1.00000	0.98444	1
112	57	2	1	1	2	10476.65	11784.95	571	B	10476.42	11203.38	571	0.99998	0.95065	1
113	58	1	1	1	1	9146.55	9253.65	889	A	9146.64	9226.90	889	1.00001	0.99711	1
114	58	1	2	1	2	8025.10	8197.82	1090	B	8025.10	8188.20	1090	1.00000	0.99883	1
115	59	2	2	1	1	39958.25	43246.95	3330	A	39958.25	42393.14	3330	1.00000	0.98026	1
116	59	2	1	1	2	38308.58	40974.08	3700	B	38308.58	39793.02	3700	1.00000	0.97118	1
117	60	1	1	1	1	9017.15	9213.94	995	A	9016.13	9180.21	995	0.99989	0.99634	1
118	60	1	2	1	2	10412.68	10975.38	1330	B	10412.68	10707.25	1330	1.00000	0.97557	1
119	61	2	2	1	1	15001.10	15404.71	1770	A	15001.10	15458.22	1770	1.00000	1.00347	1
120	61	2	1	1	2	15167.40	23557.34	1300	B	15248.63	16179.74	1300	1.00536	0.68682	1
121	62	1	1	1	1	9546.50	9636.84	813	A	9544.98	9624.18	813	0.99984	0.99869	1
122	62	1	2	1	2	10811.15	10960.05	1280	B	10811.15	10961.45	1280	1.00000	1.00013	1
123	63	2	2	1	1	17756.30	17989.39	2070	A	17756.30	17898.20	2070	1.00000	0.99493	1
124	63	2	1	1	2	15203.75	15626.44	2120	B	15203.75	15542.93	2120	1.00000	0.99466	1
125	64	1	1	1	1	7194.65	7465.33	864	A	7193.01	7391.44	864	0.99977	0.99010	1
126	64	1	2	1	2	10399.50	10716.54	1180	B	10430.32	10723.90	1180	1.00296	1.00069	1
127	65	2	2	1	1	18131.20	18217.79	2410	A	18131.20	18220.85	2410	1.00000	1.00017	1
128	65	2	1	1	2	8969.80	9084.84	995	B	8969.80	9062.19	995	1.00000	0.99751	1
129	66	1	1	1	1	10534.80	10848.77	1080	A	10534.80	10827.68	1080	1.00000	0.99806	1
130	66	1	2	1	2	12049.85	12291.84	968	B	12049.85	12194.43	968	1.00000	0.99208	1
131	67	2	2	1	1	14259.90	14959.67	1280	A	14259.90	14873.15	1280	1.00000	0.99422	1
132	67	2	1	1	2	10715.88	11470.94	1330	B	10714.58	11167.30	1330	0.99988	0.97353	1
133	68	1	1	1	1	4998.10	5209.05	528	A	4998.10	5267.38	528	1.00000	1.01120	1
134	68	1	2	1	2	5020.00	5102.14	638	B	5020.00	5111.71	638	1.00000	1.00188	1
135	69	1	1	1	1	8271.00	8713.34	1080	A	8271.00	8695.11	1080	1.00000	0.99791	1
136	69	1	2	1	2	6809.90	7269.08	612	B	6809.90	7284.80	612	1.00000	1.00216	1
137	70	2	2	1	1	12362.10	12796.00	1380	A	12362.10	12807.27	1380	1.00000	1.00088	1
138	70	2	1	1	2	6876.30	7631.18	1020	B	6876.30	7480.73	1020	1.00000	0.98028	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
139	71	1	1	1	1	9761.05	10219.33	986	A	9755.31	10101.76	986	0.99941	0.98850	1
140	71	1	2	1	2	10633.50	11371.01	837	B	10633.50	11089.42	837	1.00000	0.97524	1
141	72	2	2	1	1	5530.95	5954.81	545	A	5530.95	5660.23	545	1.00000	0.95053	1
142	72	2	1	1	2	4474.08	48297.30	320	B	4473.93	4774.50	320	0.99997	0.09886	1
143	73	2	2	1	1	14959.30	15225.17	1390	A	14959.30	15190.34	1390	1.00000	0.99771	1
144	73	2	1	1	2	10272.05	10551.13	1500	B	10272.05	10462.76	1500	1.00000	0.99162	1
145	74	1	1	1	1	5310.55	5427.17	706	A	5310.55	5432.97	706	1.00000	1.00107	1
146	74	1	2	1	2	7403.20	7769.23	1090	B	7403.20	7757.25	1090	1.00000	0.99846	1
147	75	2	2	1	1	7012.35	7128.57	807	A	7019.19	7132.52	807	1.00098	1.00055	1
148	75	2	1	1	2	5337.10	5799.32	843	B	5335.99	5815.50	843	0.99979	1.00279	1
149	76	1	1	1	1	12207.35	12701.11	994	A	12207.35	12620.97	994	1.00000	0.99369	1
150	76	1	2	1	2	6795.95	7176.15	1060	B	6795.95	7180.52	1060	1.00000	1.00061	1
151	77	1	1	1	1	7069.50	7342.04	895	A	7069.50	7348.35	895	1.00000	1.00086	1
152	77	1	2	1	2	14919.85	15004.11	1480	B	14946.43	15013.65	1480	1.00178	1.00064	1
153	78	2	2	1	1	8715.40	8850.23	888	A	8735.24	8820.85	888	1.00228	0.99668	1
154	78	2	1	1	2	7268.75	7917.34	745	B	7268.75	7952.88	745	1.00000	1.00449	1
155	79	1	1	1	1	5443.55	5772.09	711	A	5443.55	5885.85	711	1.00000	1.01971	1
156	79	1	2	1	2	5165.40	5264.71	571	B	5165.40	5275.89	571	1.00000	1.00212	1
157	80	2	2	1	1	12645.35	13610.11	1290	A	12645.35	13021.41	1290	1.00000	0.95675	1
158	80	2	1	1	2	12786.20	26180.74	970	B	12786.20	13561.28	970	1.00000	0.51799	1

4.7.3 Fed Study Data

90379 Fed REVIEWER VERIFIED CONCENTRATION DATASET

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
1	1	1	1	A	1	0	24.6	65.0	96.0	129.0	231.0	357.0	865.0	999.0	1880.0	2790	2320	1930	1190	923	553	366.0	131.0	28.1
2	1	1	2	B	1	0	0.0	133.0	427.0	899.0	1630.0	2440.0	3330.0	3290.0	3110.0	3010	2630	1770	1030	673	521	378.0	165.0	44.6
3	2	2	1	B	1	0	0.0	13.7	22.8	30.7	42.0	62.1	544.0	1610.0	2180.0	2830	2700	1940	986	634	426	321.0	181.0	33.0
4	2	2	2	A	1	0	15.6	32.1	54.3	78.7	107.0	332.0	1200.0	1590.0	2600.0	3230	2360	1470	731	514	362	266.0	165.0	39.9
5	3	2	1	B	1	0	0.0	0.0	0.0	0.0	13.7	22.5	105.0	378.0	528.0	478	1100	1610	1340	907	554	384.0	257.0	40.7
6	3	2	2	A	1	0	0.0	32.4	49.6	64.6	86.2	136.0	239.0	289.0	347.0	323	724	1120	1260	770	496	444.0	301.0	54.1
7	4	1	1	A	1	0	0.0	19.1	34.8	52.0	78.7	162.0	433.0	1750.0	2400.0	2200	1610	1240	657	416	245	150.0	58.6	10.9
8	4	1	2	B	1	0	20.8	156.0	236.0	329.0	490.0	715.0	1150.0	1670.0	1920.0	2040	1460	1090	633	369	245	153.0	50.5	0.0
9	5	1	1	A	1	0	0.0	20.9	40.2	81.0	156.0	288.0	608.0	2140.0	5150.0	7960	8090	6250	3140	2170	1060	786.0	419.0	73.0
10	5	1	2	B	1	0	21.1	95.7	180.0	395.0	985.0	1860.0	3640.0	4470.0	5700.0	7930	6880	6210	3360	2100	1150	723.0	433.0	89.6
11	6	2	1	B	1	0	0.0	0.0	84.7	257.0	481.0	742.0	1560.0	1940.0	2200.0	2000	1850	1250	664	487	229	161.0	67.8	15.2
12	6	2	2	A	1	0	32.0	297.0	469.0	704.0	1020.0	1230.0	1240.0	1330.0	1120.0	1130	915	836	610	418	265	156.0	76.3	14.1
13	7	1	1	A	1	0	106.0	547.0	632.0	657.0	730.0	650.0	1360.0	2450.0	2360.0	2440	1750	1520	645	387	245	201.0	75.9	11.0
14	7	1	2	B	1	0	0.0	136.0	329.0	970.0	1710.0	2220.0	3070.0	2640.0	2230.0	1780	1250	897	455	313	183	145.0	56.6	0.0
15	8	2	1	B	1	0	0.0	0.0	0.0	0.0	0.0	0.0	10.6	12.6	87.4	251	548	701	444	282	193	177.0	101.0	0.0
16	8	2	2	A	1	0	0.0	22.9	27.3	37.0	45.7	50.9	64.5	65.4	127.0	512	1060	950	536	305	215	188.0	95.9	0.0
17	9	1	1	A	1	0	10.8	126.0	516.0	718.0	1020.0	1150.0	1540.0	1520.0	1410.0	1160	979	763	551	401	260	172.0	83.5	17.5
18	9	1	2	B	1	0	0.0	11.0	46.3	133.0	373.0	666.0	1430.0	1560.0	1570.0	1410	1270	1400	923	519	314	238.0	97.5	22.3
19	10	2	1	B	1	0	12.7	33.1	72.3	124.0	241.0	284.0	644.0	894.0	1500.0	2600	2330	1540	705	449	229	182.0	80.7	15.7
20	10	2	2	A	1	0	24.4	40.3	70.3	127.0	434.0	758.0	1410.0	1280.0	1910.0	2100	1810	1430	655	377	225	185.0	79.4	19.9
21	11	1	1	A	1	0	0.0	41.9	86.3	135.0	201.0	331.0	575.0	712.0	773.0	789	1580	1750	1320	881	558	341.0	148.0	27.7
22	11	1	2	B	1	0	0.0	19.3	33.5	43.8	53.1	74.3	110.0	334.0	508.0	771	779	782	1080	1460	506	415.0	138.0	33.9
23	12	2	1	B	1	0	0.0	10.8	112.0	340.0	701.0	1110.0	1370.0	1290.0	1230.0	911	743	615	389	227	122	86.6	33.8	0.0
24	12	2	2	A	1	0	14.5	21.3	35.6	66.5	217.0	483.0	1030.0	1350.0	1310.0	1210	1030	793	439	282	174	101.0	43.7	0.0

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19
25	13	1	1	A	1	0	0.0	530.0	1080.0	1430.0	1710.0	2290.0	2330.0	2020.0	2070.0	1580	1430	1010	579	398	278	179.0	87.6	13.4
26	13	1	2	B	1	0	0.0	146.0	247.0	328.0	630.0	1490.0	1850.0	1990.0	1830.0	2190	1690	1350	728	435	238	201.0	65.7	17.6
27	15	1	1	A	1	0	0.0	22.7	36.2	64.6	159.0	369.0	1260.0	1660.0	1510.0	1850	2810	2120	1020	557	359	280.0	171.0	50.9
28	15	1	2	B	1	0	0.0	166.0	505.0	937.0	1130.0	1210.0	1310.0	1890.0	2210.0	2080	2200	1990	1280	826	460	278.0	180.0	36.2
29	16	2	1	B	1	0	0.0	0.0	0.0	10.2	17.0	21.2	37.1	62.6	106.0	215	371	757	1060	849	514	323.0	221.0	43.3
30	16	2	2	A	1	0	42.5	184.0	221.0	284.0	354.0	391.0	540.0	517.0	569.0	525	600	699	750	749	554	426.0	235.0	25.8
31	17	1	1	A	1	0	0.0	71.1	124.0	141.0	15.9	478.0	1320.0	1680.0	1710.0	1380	1050	891	490	257	139	94.3	30.6	0.0
32	17	1	2	B	1	0	15.5	206.0	399.0	404.0	506.0	774.0	1050.0	1500.0	1500.0	1260	796	704	354	207	112	70.9	24.3	0.0
33	18	2	1	B	1	0	0.0	0.0	0.0	10.8	166.0	19.2	49.0	281.0	530.0	688	1570	2230	1420	797	465	286.0	121.0	20.0
34	18	2	2	A	1	0	0.0	0.0	15.2	31.2	57.1	76.6	126.0	130.0	236.0	925	1330	1830	1220	820	359	248.0	98.9	17.6
35	19	1	1	A	1	0	27.9	179.0	244.0	309.0	402.0	856.0	4220.0	5520.0	4520.0	3420	3670	3000	2040	1080	655	463.0	250.0	38.4
36	19	1	2	B	1	0	0.0	27.8	52.3	95.8	138.0	183.0	844.0	2280.0	3630.0	4850	7330	5630	3800	2210	1100	774.0	345.0	53.4
37	20	2	1	B	1	0	0.0	0.0	0.0	10.6	14.2	16.6	36.9	72.8	123.0	123	183	1850	1630	837	439	247.0	153.0	22.5
38	20	2	2	A	1	0	0.0	29.7	43.3	50.2	54.1	66.8	89.4	127.0	128.0	167	316	1520	1670	738	367	268.0	140.0	23.6
39	21	2	1	B	1	0	0.0	11.3	97.7	167.0	348.0	757.0	1220.0	1700.0	1430.0	1470	1320	1090	606	446	279	191.0	86.0	14.6
40	21	2	2	A	1	0	162.0	255.0	307.0	548.0	1070.0	1230.0	3160.0	2290.0	1870.0	1670	1270	1090	846	413	296	205.0	79.9	13.8
41	22	1	1	A	1	0	19.2	93.4	158.0	214.0	267.0	290.0	379.0	1110.0	1480.0	1960	2480	2320	1640	1150	554	349.0	218.0	36.2
42	22	1	2	B	1	0	0.0	10.0	19.5	42.7	65.3	114.0	149.0	340.0	442.0	913	3820	3150	2430	1640	648	433.0	171.0	41.4
43	23	2	1	B	1	0	0.0	11.3	13.0	20.2	29.9	71.7	1090.0	2410.0	2440.0	2450	3000	2010	1400	783	384	375.0	102.0	16.0
44	23	2	2	A	1	0	121.0	974.0	1100.0	1440.0	1430.0	1350.0	2100.0	1740.0	1540.0	1620	1700	1290	650	427	255	168.0	62.3	11.0
45	24	1	1	A	1	0	42.6	540.0	1080.0	1200.0	1090.0	1020.0	1050.0	866.0	737.0	736	594	478	298	187	105	61.1	46.1	0.0
46	24	1	2	B	1	0	34.9	451.0	941.0	1030.0	994.0	893.0	845.0	702.0	594.0	761	890	860	436	277	178	88.3	40.2	0.0

90379 Fed REVIEWER-CALCULATED PHARMACOKINETIC DATASET

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
1	1	1	1	1	1	19000.45	19174.42	2790	6.0	4.29128	0.16152
2	1	2	1	2	1	23964.35	24340.16	3330	4.5	5.84063	0.11868
3	2	1	2	2	1	16762.58	17188.62	3230	6.0	7.40128	0.09365
4	2	2	2	1	1	18095.08	18416.81	2830	6.0	6.75786	0.10257

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
5	3	1	2	2	1	14240.85	14980.05	1260	10.0	9.47089	0.07319
6	3	2	2	1	1	15291.80	15690.07	1610	8.0	6.78279	0.10219
7	4	1	1	1	1	11946.38	12013.42	2400	5.5	4.26332	0.16258
8	4	2	1	2	1	11781.30	12083.42	2040	6.0	4.14676	0.16715
9	5	1	1	1	1	50313.28	50874.09	8090	7.0	5.32501	0.13017
10	5	2	1	2	1	53958.48	54656.90	7930	6.0	5.40301	0.12829
11	6	1	2	2	1	11361.05	11460.24	1330	5.0	4.87620	0.14215
12	6	2	2	1	1	13515.75	13611.96	2200	5.5	4.38739	0.15799
13	7	1	1	1	1	15441.85	15524.68	2450	5.0	5.21922	0.13281
14	7	2	1	2	1	13680.80	14089.22	3070	4.5	5.00173	0.13858
15	8	1	2	2	1	6708.28	7730.78	1060	7.0	7.39045	0.09379
16	8	2	2	1	1	5114.55	6352.12	701	8.0	8.49328	0.08161
17	9	1	1	1	1	11550.80	11685.23	1540	4.5	5.32462	0.13018
18	9	2	1	2	1	13492.70	13656.21	1570	5.5	5.08223	0.13639
19	10	1	2	2	1	13173.28	13331.77	2100	6.0	5.52071	0.12555
20	10	2	2	1	1	13366.18	13481.22	2600	6.0	5.07900	0.13647
21	11	1	1	1	1	15784.03	15970.07	1750	8.0	4.65536	0.14889
22	11	2	1	2	1	13763.98	13948.32	1460	12.0	3.76917	0.18390
23	12	1	2	2	1	8094.13	8374.61	1350	5.0	4.44888	0.15580
24	12	2	2	1	1	7635.95	7854.47	1370	4.5	4.48121	0.15468
25	13	1	1	1	1	15653.80	15759.23	2330	4.5	5.45351	0.12710
26	13	2	1	2	1	14508.40	14624.08	2190	6.0	4.55589	0.15214
27	15	1	1	1	1	17537.83	18072.37	2810	7.0	7.27938	0.09522
28	15	2	1	2	1	20558.70	20850.06	2210	5.5	5.57892	0.12424
29	16	1	2	2	1	12882.05	13150.48	750	10.0	7.21173	0.09611
30	16	2	2	1	1	11281.60	11674.42	1060	10.0	6.28829	0.11023
31	17	1	1	1	1	8764.93	8940.39	1710	5.5	3.97458	0.17439
32	17	2	1	2	1	7986.95	8124.80	1500	5.0	3.93217	0.17628
33	18	1	2	2	1	12783.50	12887.59	1830	8.0	4.09923	0.16909

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
34	18	2	2	1	1	14682.50	14810.75	2230	8.0	4.44488	0.15594
35	19	1	1	1	1	32241.55	32563.70	5520	5.0	5.81497	0.11920
36	19	2	1	2	1	46378.30	46736.10	7330	7.0	4.64429	0.14925
37	20	1	2	2	1	11916.53	12095.08	1670	10.0	5.24433	0.13217
38	20	2	2	1	1	12480.30	12642.35	1850	8.0	4.99216	0.13885
39	21	1	2	2	1	15085.15	15185.18	3160	4.5	5.02446	0.13795
40	21	2	2	1	1	11810.93	11918.47	1700	5.0	5.10580	0.13576
41	22	1	1	1	1	21034.95	21307.06	2480	7.0	5.21029	0.13303
42	22	2	1	2	1	24463.40	24693.48	3820	7.0	3.85222	0.17993
43	23	1	2	2	1	15566.70	15635.82	2100	4.5	4.35559	0.15914
44	23	2	2	1	1	19509.38	19608.54	3000	7.0	4.29582	0.16135
45	24	1	1	1	1	7623.85	8027.57	1200	3.0	6.07019	0.11419
46	24	2	1	2	1	8739.85	8985.43	1030	3.0	4.23439	0.16369

4.7.4 Fed Study Output

Fed STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
SUB	23	1 2 3 4 5 6 7 8 9 10 11 12 13 15 16 17 18 19 20 21 22 23 24
TRT	2	1 2
PER	2	1 2
SEQ	2	1 2

Number of Observations Read	46
Number of Observations Used	46

Fed STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	24	10.20445644	0.42518568	33.02	<.0001
Error	21	0.27038660	0.01287555		
Corrected Total	45	10.47484303			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.974187	1.183845	0.113470	9.584908

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	1.27136595	1.27136595	98.74	<.0001
SUB(SEQ)	21	8.90454537	0.42402597	32.93	<.0001
PER	1	0.01346990	0.01346990	1.05	0.3180
TRT	1	0.01507522	0.01507522	1.17	0.2915

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.27136595	1.27136595	98.74	<.0001
SUB(SEQ)	21	8.90454537	0.42402597	32.93	<.0001
PER	1	0.01223498	0.01223498	0.95	0.3408
TRT	1	0.01507522	0.01507522	1.17	0.2915

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.27136595	1.27136595	3.00	0.0980

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.03624047	0.03349229	-1.08	0.2915

Fed STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	24	9.61634441	0.40068102	34.47	<.0001
Error	21	0.24412474	0.01162499		
Corrected Total	45	9.86046915			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.975242	1.122389	0.107819	9.606223

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	1.17963732	1.17963732	101.47	<.0001
SUB(SEQ)	21	8.40641701	0.40030557	34.43	<.0001
PER	1	0.01271992	0.01271992	1.09	0.3074
TRT	1	0.01757015	0.01757015	1.51	0.2325

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.17963732	1.17963732	101.47	<.0001
SUB(SEQ)	21	8.40641701	0.40030557	34.43	<.0001
PER	1	0.01143035	0.01143035	0.98	0.3327
TRT	1	0.01757015	0.01757015	1.51	0.2325

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.17963732	1.17963732	2.95	0.1008

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.03912458	0.03182425	-1.23	0.2325

Fed STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	24	12.39904922	0.51662705	12.94	<.0001
Error	21	0.83831157	0.03991960		
Corrected Total	45	13.23736080			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.936671	2.611241	0.199799	7.651491

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	1.78495620	1.78495620	44.71	<.0001
SUB(SEQ)	21	10.58252881	0.50392994	12.62	<.0001
PER	1	0.00851659	0.00851659	0.21	0.6489
TRT	1	0.02304762	0.02304762	0.58	0.4558

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.78495620	1.78495620	44.71	<.0001
SUB(SEQ)	21	10.58252881	0.50392994	12.62	<.0001
PER	1	0.00976119	0.00976119	0.24	0.6261
TRT	1	0.02304762	0.02304762	0.58	0.4558

Tests of Hypotheses Using the Type III MS for SUB(SEQ) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1.78495620	1.78495620	3.54	0.0738

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.04481001	0.05897325	-0.76	0.4558

90379 Fed FIRM TO REVIEWER RATIO

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	1	1	1	1	1	19000.45	19174.42	2790	A	19007.62	19200.72	2790	1.00038	1.00137	1
2	1	1	2	1	2	23964.35	24340.16	3330	B	23964.35	24349.75	3330	1.00000	1.00039	1
3	2	2	2	1	1	16762.58	17188.62	3230	A	16762.58	17143.92	3230	1.00000	0.99740	1
4	2	2	1	1	2	18095.08	18416.81	2830	B	18102.49	18374.56	2830	1.00041	0.99771	1
5	3	2	2	1	1	14240.85	14980.05	1260	A	14240.85	14748.56	1260	1.00000	0.98455	1
6	3	2	1	1	2	15291.80	15690.07	1610	B	15285.23	15612.32	1610	0.99957	0.99504	1
7	4	1	1	1	1	11946.38	12013.42	2400	A	11946.38	12018.68	2400	1.00000	1.00044	1
8	4	1	2	1	2	11781.30	12083.42	2040	B	11781.30	12071.14	2040	1.00000	0.99898	1
9	5	1	1	1	1	50313.28	50874.09	8090	A	50272.03	50814.23	8090	0.99918	0.99882	1
10	5	1	2	1	2	53958.48	54656.90	7930	B	53958.48	54671.47	7930	1.00000	1.00027	1
11	6	2	2	1	1	11361.05	11460.24	1330	A	11361.05	11462.06	1330	1.00000	1.00016	1
12	6	2	1	1	2	13515.75	13611.96	2200	B	13515.75	13625.03	2200	1.00000	1.00096	1
13	7	1	1	1	1	15441.85	15524.68	2450	A	15441.85	15515.75	2450	1.00000	0.99942	1
14	7	1	2	1	2	13680.80	14089.22	3070	B	13680.80	14072.47	3070	1.00000	0.99881	1
15	8	2	2	1	1	6708.28	7730.78	1060	A	6708.28	7563.72	1060	1.00000	0.97839	1
16	8	2	1	1	2	5114.55	6352.12	701	B	5114.55	6150.83	701	1.00000	0.96831	1
17	9	1	1	1	1	11550.80	11685.23	1540	A	11550.80	11686.15	1540	1.00000	1.00008	1
18	9	1	2	1	2	13492.70	13656.21	1570	B	13492.70	13663.97	1570	1.00000	1.00057	1
19	10	2	2	1	1	13173.28	13331.77	2100	A	13173.28	13337.72	2100	1.00000	1.00045	1
20	10	2	1	1	2	13366.18	13481.22	2600	B	13366.18	13482.23	2600	1.00000	1.00008	1
21	11	1	1	1	1	15784.03	15970.07	1750	A	15784.03	15977.06	1750	1.00000	1.00044	1
22	11	1	2	1	2	13763.98	13948.32	1460	B	13763.98	13992.57	1460	1.00000	1.00317	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
23	12	2	2	1	1	8094.13	8374.61	1350	A	8094.13	8361.70	1350	1.00000	0.99846	1
24	12	2	1	1	2	7635.95	7854.47	1370	B	7635.95	7836.45	1370	1.00000	0.99771	1
25	13	1	1	1	1	15653.80	15759.23	2330	A	15653.80	15748.65	2330	1.00000	0.99933	1
26	13	1	2	1	2	14508.40	14624.08	2190	B	14508.40	14640.82	2190	1.00000	1.00114	1
27	15	1	1	1	1	17537.83	18072.37	2810	A	17537.83	18065.37	2810	1.00000	0.99961	1
28	15	1	2	1	2	20558.70	20850.06	2210	B	20558.70	20850.21	2210	1.00000	1.00001	1
29	16	2	2	1	1	12882.05	13150.48	750	A	12882.05	13065.97	750	1.00000	0.99357	1
30	16	2	1	1	2	11281.60	11674.42	1060	B	11281.60	11646.09	1060	1.00000	0.99757	1
31	17	1	1	1	1	8764.93	8940.39	1710	A	8764.93	8926.29	1710	1.00000	0.99842	1
32	17	1	2	1	2	7986.95	8124.80	1500	B	7986.95	8117.16	1500	1.00000	0.99906	1
33	18	2	2	1	1	12783.50	12887.59	1830	A	12783.50	12897.82	1830	1.00000	1.00079	1
34	18	2	1	1	2	14682.50	14810.75	2230	B	14682.50	14814.31	2230	1.00000	1.00024	1
35	19	1	1	1	1	32241.55	32563.70	5520	A	32241.55	32524.26	5520	1.00000	0.99879	1
36	19	1	2	1	2	46378.30	46736.10	7330	B	46378.30	46733.76	7330	1.00000	0.99995	1
37	20	2	2	1	1	11916.53	12095.08	1670	A	11916.53	12088.52	1670	1.00000	0.99946	1
38	20	2	1	1	2	12480.30	12642.35	1850	B	12480.30	12636.64	1850	1.00000	0.99955	1
39	21	2	2	1	1	15085.15	15185.18	3160	A	15085.15	15181.04	3160	1.00000	0.99973	1
40	21	2	1	1	2	11810.93	11918.47	1700	B	11813.44	11916.98	1700	1.00021	0.99987	1
41	22	1	1	1	1	21034.95	21307.06	2480	A	21034.95	21301.42	2480	1.00000	0.99974	1
42	22	1	2	1	2	24463.40	24693.48	3820	B	24463.40	24747.81	3820	1.00000	1.00220	1
43	23	2	2	1	1	15566.70	15635.82	2100	A	15566.70	15639.01	2100	1.00000	1.00020	1
44	23	2	1	1	2	19509.38	19608.54	3000	B	19509.38	19608.70	3000	1.00000	1.00001	1
45	24	1	1	1	1	7623.85	8027.57	1200	A	7625.35	7969.44	1200	1.00020	0.99276	1
46	24	1	2	1	2	8739.85	8985.43	1030	B	8739.85	8975.36	1030	1.00000	0.99888	1

4.8 Additional Attachments

APPEARS THIS WAY ON ORIGINAL

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090379

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Budesonide Capsules, 3 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and has no further questions.

We acknowledge that you will conduct your dissolution testing using the following dissolution method:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37°C		**Volume**
Acid stage	First 2 hours	0.1 N HCl	1000 mL
Buffer stage	1-6 hours	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, and 6 hours		

And your test product will meet the following Specifications:

Acid stage:

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.9 Outcome Page

ANDA: 090379

Enter Review Productivity and Generate Report

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14711	1/31/2008	Bioequivalence Study	Fasting Study	1	1
14711	1/31/2008	Bioequivalence Study	Fed Study	1	1
14711	1/31/2008	Other	DSI Inspection Report	1	1
14711	7/26/2011	Other	Study Amendment Without Credit (WC)	0	0
				Bean Total:	3

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

/s/

HARITHA MANDULA
08/09/2011

BING V LI
08/10/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/10/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90-379	
Drug Product Name	Budesonide Capsule (RLD: Entocort® EC)	
Strength (s)	3 mg	
Applicant Name	Barr Laboratories, Inc.	
Address[1]	225 Summit Avenue, Montvale, NJ 07645-1523	
Applicant's Point of Contact	Nicholas Tantillo	
Contact's Phone Number	201-930-3650	
Contact's Fax Number	201-930-3318	
Original Submission Date(s)	January 31, 2008	
Submission Date(s) of Amendment(s) Under Review	February 9, 2009 (Response to deficiency letter dated: July 30, 2008)	
First Generic	Yes	
Reviewer	Om Anand	
Study Number (s)	10716217	10716218
Study Type (s)	Fasting	Non-Fasting
Strength(s)	3 mg	3 mg
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	3320 Walnut Bend Lane Houston, Texas 77042-4712 832-251-8100	
Analytical Site	(b) (4)	
Analytical Address		
OUTCOME DECISION	Acceptable	

Review of a Dissolution Amendment

[1] In the previous communications, the firm address was: 223 Quaker Road P.O Box 2900 Pomona, NY 10970. However, the phone number and the fax number remain the same.

I. EXECUTIVE SUMMARY

This is a review of dissolution amendment only.

The firm has submitted the current amendment to address the deficiencies identified in the FDA Bioequivalence Deficiency letter dated July 30, 2008.

There is no USP method for this product but there is a FDA-recommended method.

The firm conducted dissolution testing with its own proposed method. The firm's proposed dissolution method is acceptable. However, the firm's proposed specifications for the buffer stage are (b) (4) and not supported by the data and therefore not acceptable. Based on the data, the DBE recommended more stringent specifications which the firm's test product passes at the A1 level at acid stage and L1 level[2] at buffer stage.

In this amendment, the firm has accepted and acknowledged the DBE recommended dissolution method and specifications. The firm has requested a change in the sampling time points which is acceptable. The firm's responses to the other dissolution related deficiencies are satisfactory and acceptable.

The firm also conducted and submitted comparative dissolution testing in three additional media: (pH 1.2, pH 4.5 and pH 6.8). There is no evidence of dose-dumping.

The Long Term Storage Stability (LTSS) is sufficient to cover the maximum storage time of the study samples.

The firm provided the SAS files in the electronic format for both BE biostudies.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

---

2 (b) (4)

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐

Note: This is first generic application. There is no dissolution method available in USP/FDA-external data base/DBE- internal database. The RLD dissolution method is using USP apparatus 4.

The firm has used its own proposed method.

RLD dissolution method:[3]

Drug release at pH 1.2: In USP apparatus 4 with 12 mm flow-through cells at 8 mL/min and 37ºC.
Performed on one composite sample consisting of the contents from 8 capsules.

Specifications at pH 1.2: NMT (b) (4)% of labeled content after 2 hrs.

Drug release at pH 7.5: In USP Apparatus 4 with 12 mm flow-through cells at 8 mL/min and 37ºC.

Specifications at pH 7.5:
After 1 hr (b) (4)% of labeled content
After 2 hr % of labeled content
After 4 hr % of labeled content

[3] v:\\firmsan (b) (4)\controls\03057c0103.doc and Dissolution_DFS_N02134 N 000 C 30 Mar-2001

After 8 hr NLT (b)(4)% of labeled content

The media used are simulated gastric fluid (pH 1.2) for the acid stage and simulated intestinal fluid (pH 7.5) for the buffer stage.

Firm's proposed method:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37ºC		**Volume**
First 2 hours;	Acid stage	0.1 N HCl	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, 6,and 8 hours		

Firm's Proposed Specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b)(4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b)(4)%
2	%
4	%
6	NLT (b)(4)%

Data driven DBE-recommended specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b)(4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b)(4)%
2	%
4	%
6	NLT (b)(4)%

II. REVIEW OF THE CURRENT SUBMISSION

Deficiency 1:

You stated that you used 0.01 N HCl as the acid stage dissolution medium in the in vitro - in vivo correlation study report in the fasting study Clinical Study Report (Module 5.3.1.3, page # 660) and in the Summary Table for In vitro Dissolution Studies. But in the same in vitro - in vivo correlation study report (Module 5.3.1.3, page # 665) and in the analytical method validation report (located in Module 3.2, page # 221) you stated that 0.1 N HCI was used as the acid stage dissolution medium. Please clarify which medium, 0.1 N or 0.01 N HCI, was used in the acid stage dissolution study.

Firm's Response:

0.1 N HCI was used as the medium in the acid stage dissolution study. Please note that the reference to 0.01 N HCI as the acid stage dissolution medium in the in vitro - in vivo correlation study report in the fasting study Clinical Study Report (Module 5.3.1.3, page # 660) and in the Summary Table for In vitro Dissolution Studies was a typographical error.

Reviewer's Comment:

The firm has stated that 0.1 N HCl was used in acid stage of the dissolution. The firm's response is satisfactory.

Deficiency 2:

You conducted dissolution testing in pH 4.5 and pH 6.8 media. Please clarify the type of buffers (acetate or phosphate) used for the two dissolution media.

Firm's Response:

Dissolution testing was conducted in pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Please see the updated Special Studies Report: Dissolution of Budesonide EC Capsules, 3 mg in various dissolution media (ARD_RPT-3041, Version 2.0), which clarifies pH 4.5 acetate buffer and pH 6.8 phosphate buffer were used for dissolution testing.

Reviewer's Comment:

The firm stated that it used pH 4.5 acetate buffer and pH 6.8 phosphate buffer for additional dissolution testing. This is acceptable; the firm's response is satisfactory.

Deficiency 3:

The DBE agrees that the dissolution testing should be conducted using the two-stage dissolution method as proposed by you:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature:** 37°C		**Volume**
First 2 hours	Acid stage	0.1 N HCl or 0.01 N HCl, pending clarification	1000 mL
1-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4 and 6 hours		

However, DBE finds your proposed buffer stage dissolution specifications of 1 hr: (b) (4) (b) (4)%; 2 hrs: (b) (4)%; 4 hrs: (b) (4)%; and 6 hrs: NLT (b) (4)% for your test product as (b) (4) (b) (4). Based on the dissolution testing data submitted by you, DBE is recommending the following dissolution specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4)%

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4)%
2	%
4	%
6	NLT (b) (4)%

Please acknowledge that you will conduct the dissolution testing for the test product using the above dissolution method and the DBE-recommended specifications.

Firm's Response:

Barr Laboratories, Inc. acknowledges using the above DBE-recommended specifications. However, please note that there was a typographical error in the dissolution method table above regarding the buffer stage from 1-10 hours, which should be 1-6 hours. Please see below for the updated dissolution method table.

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature:** 37˚C		**Volume**
First 2 hours	Acid stage	0.1 N HCl	1000 mL
1-6 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4 and 6 hours		

Please see Module 3.2.P.5 for details.

Reviewer's Comment:

The firm has previously conducted and submitted the dissolution data for 2 hours in acid (0.1 N HCl) followed by for 1-8 hours in phosphate buffer pH 7.5. The specifications were set up to 6 hours. The firm is inclined to conduct two-stage dissolution testing as follows:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature:** 37˚C		**Volume**
First 2 hours	Acid stage	0.1 N HCl	1000 mL
1-6 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4 and 6 hours		

This firm's proposed change in the dissolution sample time points is acceptable. The firm has accepted and acknowledged the DBE recommended method and specifications. The firm's response is satisfactory.

III. OVERALL COMMENTS:

1. The firm has satisfactorily responded to all deficiencies. The firm should conduct the dissolution as follows:

Method:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37ºC		**Volume**
Acid stage	First 2 hours	0.1 N HCl	1000 mL
Buffer stage	1-6 hours	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, and 6 hours		

Specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

IV. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Barr Laboratories, Inc. on its test product, Budesonide Capsule 3 mg, comparing it with the reference listed drug product, Astra Zeneca's Entocort® EC, 3 mg, is **acceptable.**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-379

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Budesonide Capsule, 3 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later.

We concur that you have acknowledged the DBE-recommended dissolution method and specification as follows:

Method:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37°C		**Volume**
Acid stage	First 2 hours	0.1 N HCl	1000 mL
Buffer stage	1-6 hours	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, and 6 hours		

Specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 90-379

Reviewer: Anand, Om **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Budesonide Enteric Coated Capsule

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7597	2/9/2009	Other	Dissolution Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
Study Amendment Dissolution data	1
Study Amendment Total	1

Grand Total	**1**

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

/s/

Om Anand
3/4/2009 06:17:58 PM
BIOPHARMACEUTICS

Xiaojian Jiang
3/4/2009 09:19:11 PM
BIOPHARMACEUTICS

Moheb H. Makary
3/5/2009 07:37:33 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90-379	
Drug Product Name	Budesonide Enteric Coated Capsule (RLD: Entocort® EC)	
Strength (s)	3 mg	
Applicant Name	Barr Laboratories, Inc.	
Address	223 Quaker Road P.O Box 2900 Pomona, NY 10970	
Applicant's Point of Contact	Nicholas Tantillo, Sr. Director Regulatory Affairs	
Contact's Phone Number	201-930-3650	
Contact's Fax Number	201-930-3318	
Submission Date(s)	January 31, 2008	
First Generic	Yes	
Reviewer	Om Anand, Ph.D.	
Study Number (s)	10716217	10716218
Study Type (s)	Fasting	Non-Fasting
Strength(s)	3 mg	3 mg
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	3320 Walnut Bend Lane Houston, Texas 77042-4712 (832) 251-8100	
Analytical Site	(b) (4)	
Analytical Site Address		
OUTCOME DECISION	**Incomplete**	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP or FDA-recommended dissolution testing method for this test product.

The firm conducted dissolution testing with its own proposed method. The firm's proposed dissolution method is acceptable. However, the Division of Bioequivalence (DBE) deems the firm's proposed dissolution specifications for the buffer stage as (b) (4) (b) (4) and based on the firm's submitted dissolution data, recommends the following specifications for the buffer stage: 1 hr: (b) (4)%; 2 hrs: (b) (4)%; 4 hrs: (b) (4)%; and 6 hrs: NLT (b) (4)%. The firm's test product passes the acid stage specification at the A1 level and the buffer stage specifications at the L1 level[1]. The firm should indicate if it accepts the DBE-recommended specifications.

The firm also conducted and submitted comparative dissolution testing in three additional media: (pH 1.2, pH 4.5 and pH 6.8). There is no evidence of dose-dumping of the test product.

The Long Term Storage Stability (LTSS) is sufficient to cover the maximum storage time of the study samples for both the bioequivalence (BE) studies.

The firm provided the SAS files in the electronic format for both the BE studies.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The DBE will review the fasted and fed BE studies at a later date.

---

1 (b) (4)

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐

Note: This is first generic application. There is no dissolution method available in the FDA-external data base or the DBE- internal database. The RLD dissolution method used USP apparatus 4.

The firm proposed its own dissolution method and specifications.

RLD dissolution method and specifications:[2]

Drug release at pH 1.2: In USP apparatus 4 with 12 mm flow-through cells at 8 mL/min and 37ºC. Dissolution conducted on one composite sample consisting of the contents from 8 capsules.

Specifications at pH 1.2: NMT (b)(4)% of labeled content after 2 hrs.

Drug release at pH 7.5: In USP Apparatus 4 with 12 mm flow-through cells at 8 mL/min and 37ºC.

Specifications at pH 7.5:

After 1 hr	(b)(4)% of labeled content
After 2 hr	% of labeled content
After 4 hr	% of labeled content
After 8 hr	NLT (b)(4)% of labeled content

[2] v:\\firmsan(b)(4)\controls\03057c0103.doc and Dissolution_DFS_N02134 N 000 C 30 Mar-2001

The media used are simulated gastric fluid (pH 1.2) for the acid stage and simulated intestinal fluid (pH 7.5) for the buffer stage.

Firm's proposed method:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37ºC		**Volume**
First 2 hours;	Acid stage	0.1 N HCl	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, 6,and 8 hours		

Firm's Proposed Specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

DBE-recommended specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Table 2.1: Dissolution in Acid stage and Buffer stage (Firm's proposed method).

Dissolution Conditions	**Apparatus:**	Apparatus II (paddles) with capsule sinker
	Speed of Rotation:	75 rpm
	Medium:	Medium 1: 0.1 N HCl[3] (first 2 hours); Medium 2: pH 7.5 phosphate buffer[4] (2-10 hours)
	Volume:	1000 mL
	Temperature:	37.0 ± 0.5 °C
Firm's Proposed Specifications[5]	Acid stage	2 hours: NMT (b) (4)%
	Buffer stage	1 hour: (b) (4) 2 hours % 4 hours % 6 hours: NLT (b) (4)%
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc., 223 Quaker Road, Pomona, NY 10970	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)						Study Report Location
						2 hours	1 hour	2 hours	4 hours	6 hours	8 hours	
						Medium 1: 0.1[2]N HCl (First 2 hours) Acid Stage	Medium 2: pH 7.5 phosphate buffer[3] (2-10 hours) (Buffer Stage)					
ARD_RPT - 3041	9/28/07	Test: Budesonide Enteric Coated Capsule Lot No. 800206; Mfr Date: 9/9/07	3mg Capsule	12	Mean	1	37	56	77	88	93	Barr Laboratories, Inc.
					Range[6]		(b) (4)					
					%CV	0.0	6.4	5.6	3.2	2.4	2.3	
	3/28/07	Reference: Entocort EC Lot No. NC0077 Exp. Date: 11/30/09	3mg Capsule	12	Mean	1	53	73	92	97	98	
					Range		(b) (4)					
					%CV	0.0	4.4	2.8	1.6	2.3	2.7	

[3] The summary tables (and module 5.3-660) mentioned the media as 0.01 N HCl. The dissolution method in module 3.2.P.5-221 and module 5.3-665 mentioned the media as 0.1 N HCl.

[4] The summary tables mentioned the media as solution. It should be buffer as mentioned in module 3.2.P.5-222.

[5] The specifications provided in the summary biotable are: Less than (b) (4)% in 0.1 N HCl in 2 hrs and in pH 4.5 phosphate buffer (up to 8 hours). The specifications presented here were provided in module 3.2.P.5, page 289.

[6] The reviewer noted that some of the range values provided by the firm in the dissolution summary biotable were not accurate and, therefore, corrected the range values in the above table, based on the dissolution raw data provided by the firm.

Figure 1: Dissolution profile comparison between test and reference product (in Acid stage and Buffer stage)

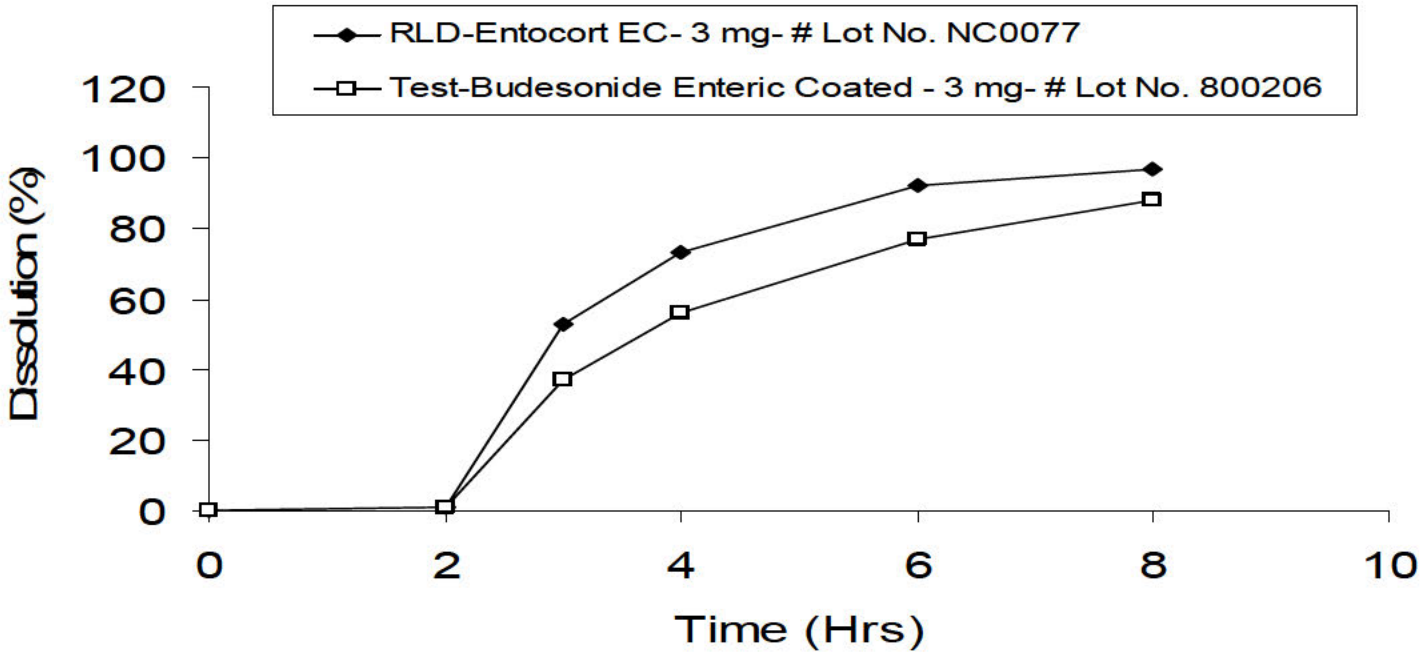


Table 2.2: Dissolution data in 0.1 N HCl (pH 1.2)[7]

Sample No.	Biobatch: 800206	RLD: NC0077
	% Dissolved - 2 hours	
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean	**1**	**1**
High	(b) (4)	
Low		

Table 2.3: Dissolution data in pH 4.5 buffer[8]

	Biobatch: 800206					RLD: NC0077				
Time (hour)	1	2	4	6	8	1	2	4	6	8
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	**2**	**3**	**4**	**6**	**7**	**0**	**1**	**2**	**2**	**3**
High	(b) (4)									
Low										

[7] Module 5.3-675.
[8] Module 5.3-676 The type of buffer has not been mentioned

Table 2.4: Dissolution data in pH 6.8 Buffer [9]

	Biobatch: 800206					RLD: NC0077				
Time (hour)	1	2	4	6	8	1	2	4	6	8
1										(b) (4)
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	**34**	**51**	**71**	**83**	**90**	**45**	**70**	**91**	**97**	**98**
High										(b) (4)
Low										
RSD	5.9	4.3	2.7	2.6	2.1	4.0	2.6	2.1	3.1	3.0

[9] Module 5.3 – 677. The type of buffer has not been mentioned.

II. COMMENTS:

1. The firm conducted dissolution with its own proposed method. The RLD used a two stage dissolution method using USP apparatus 4 with flow-through cells. The RLD also conducted dissolution testing on one composite sample consisting of the contents from 8 capsules. The firm is using individual units for conducting the dissolution testing.

2. The firm's proposed two stage dissolution method as given below is acceptable:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37ºC		**Volume**
First 2 hours	Acid stage	0.1 N HCl	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, 6,and 8 hours		

3. The firm also conducted acceptable comparative dissolution testing in two additional media: pH 4.5 and pH 6.8. However, it is not clear what type buffers (acetate or phosphate) were used. The firm conducted dissolution testing in 0.1 N HCl for the duration of only 2 hours, similar to the acid stage dissolution testing.

4. The reviewer noted that the 90% CI for both the bioequivalence studies are within the acceptable range of 80-125% although the data of the BE studies have not been verified.

5. The firm submitted long term frozen sample storage stability data for 525 days at -20°C, which exceeds the storage period of biostudy samples for both the fasting and the fed bioequivalence study.

6. The firm submitted all the required summary bio-tables which are located in module 5.

7. The SAS files are present for all the studies and are located in module 5.

III. DEFICIENCY COMMENTS:

1. The firm stated that it used **0.01 N HCl** as the acid stage dissolution medium in the in vitro-in vivo correlation study report in the fasting study Clinical Study Report (Module 5.3.1.3, page # 660) and in the Summary Biotable for In vitro Dissolution Studies. But in the same in vitro-in vivo correlation study report (Module 5.3.1.3, page # 665) and in the analytical method validation report (located in Module 3.2,

page # 221) the firm stated that **0.1N** HCl was used as the acid stage dissolution medium. The firm should clarify which medium, 0.1 N or 0.01 N HCl, was used in the acid stage dissolution study.

2. The firm conducted dissolution testing in pH 4.5 and pH 6.8 media. The firm should clarify the type of buffer (acetate or phosphate) used for the two dissolution media.

3. DBE agrees that the dissolution testing should be conducted using the following method:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37ºC		**Volume**
First 2 hours;	Acid stage	0.1 N HCl	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, 6,and 8 hours		

DBE deems firm's proposed buffer stage dissolution specifications of 1 hr: (b) (4)%; 2 hrs: (b) (4)%; 4 hrs: (b) (4)%; and 6 hrs: NLT (b) (4)% for its test product as (b) (4). Based on the dissolution testing data submitted by the firm, DBE is recommending the following dissolution specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4)%

The firm should indicate if it accepts the DBE-recommended specifications.

IV. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Barr Laboratories, Inc. on its test product, Budesonide Enteric Coated Capsule 3 mg, comparing it with the reference listed drug product, Astra Zeneca Entocort® EC, 3 mg, is **incomplete** for the deficiency comments mentioned above.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-379

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Budesonide Enteric Coated Capsule, 3 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. You stated that you used **0.01 N HCl** as the acid stage dissolution medium in the in vitro - in vivo correlation study report in the fasting study Clinical Study Report (Module 5.3.1.3, page # 660) and in the Summary Table for In vitro Dissolution Studies. But in the same in vitro - in vivo correlation study report (Module 5.3.1.3, page # 665) and in the analytical method validation report (located in Module 3.2, page # 221) you stated that **0.1N** HCl was used as the acid stage dissolution medium. Please clarify which medium, 0.1 N or 0.01 N HCl, was used in the acid stage dissolution study.

2. You conducted dissolution testing in pH 4.5 and pH 6.8 media. Please clarify the type of buffers (acetate or phosphate) used for the two dissolution media.

3. The DBE agrees that the dissolution testing should be conducted using the two-staged dissolution method as proposed by you:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37°C		**Volume**
First 2 hours;	Acid stage	0.1 N HCl or 0.01 N HCl, pending clarification	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4 and 6 hours		

However, the DBE finds your proposed buffer stage dissolution specifications of 1 hr: (b) (4)%; 2 hrs: (b) (4)%; 4 hrs: (b) (4)%; and 6 hrs: NLT (b) (4)% for your test product as (b) (4). Based on the dissolution testing data submitted by you, the DBE is recommending the following dissolution specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT (b) (4) %

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	(b) (4) %
2	%
4	%
6	NLT (b) (4) %

Please acknowledge that you will conduct the dissolution testing for the test product using the above dissolution method and the FDA-recommended specifications.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 90-379

Reviewer: Anand, Om **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Dissolution Review Budesonide Enteric Coated Capsule

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
6034	1/31/2008	Dissolution Data	Dissolution Review	1	1	Edit	Delete
				Bean Total:	1		

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

/s/

Joan Zhao
7/25/2008 10:46:06 AM
BIOPHARMACEUTICS
For Om Anand

Parthapratim Chandaroy
7/25/2008 10:56:18 AM
BIOPHARMACEUTICS
for Paul Seo

Hoainhon T. Nguyen
7/25/2008 11:34:07 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090379

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: II	Team: 21	PM: Erin Lee

Electronic ANDA: Yes ☒ No ☐

ANDA #:090379
Firm Name:Barr Laboratories, Inc., an indirect and wholly owned subsidiary of Teva Pharmaceuticals USA
ANDA Name:Budesonide Capsules, 3 mg
RLD Name:Entocort EC Capsules, 3 mg

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 21\Electronic AP-TA-NAcGMPSummaries

AP/TA Letter Located:
V:\Chemistry Division II\Team 21\AP TA NAcGMP CR WD Letters

Project Manager Evaluation: **Date: 4/16/13 Initials:** EL

☐ Previously reviewed and tentatively approved --- Date _____
☒ Previously reviewed and CGMP Complete Response issued -- Date 4/3/12

Original Rec'd date 2/1/08	Date of Application 1/31/08	Date Acceptable for Filing 4/7/08
Patent Certification (type) P IV	Date Patent/Excl. expires 1/1/15	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☒ Pending ☐☐ ☐ Acceptable ☐ OAI *EES Date Acceptable:* _____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 6/16/11 Addendum Needed: Yes ☒ No ☐ Comment: CMC/DMF amendment review
Date of Acceptable Bio 8/10/11 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 4/17/13 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) _____

Methods Val. Samples Pending: Yes ☐ No ☐**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 4/17/13 & 9/23/13 &1/9/14 &4/1/14 REMS Required: Yes ☐ No ☐ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 4/17/13

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

☐ Office of Management, API/FDF facility list provided.

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

Reference ID: 3482222

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 4/17/2013**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☐ If yes, has it been completed	RLD = Entocort EC NDA# 21-324 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒☐	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 2/1/2008, BOS=Entocort EC NDA 21-324, PIV to '602 and '340. ANDA ack for filing with a PIV on 2/1/2008 (LO dated 4/7/2008). Patent Amendment rec'd on 1/13/2009-RR from AstraZeneca LP in Wilmington DE signed and dated 4/14/2008, RR from Aktiebolaget Draco in Lund Sweden signed and dated 4/21/2008, notice sent via (b) (4) to Aktiebolaget Draco in Sodertalje Sweden with notice delivered on 4/14/2008, notice sent via (b) (4) (b) (4) to AZ in Wilmington DE with notice delivered on 4/11/2008. Patent Amendment rec'd on 2/10/2009-CA 08-305 filed in the D of DE on 5/23/2008 for infringement of the '340 and '602 patents. Patent Amendment rec'd on 12/1/2010-on 5/21/2010 CA 08-305 was dismissed with prejudice with the dismissal including a clause that Barr was enjoined from infringing the '340 and '602 patents until 2/15/2012. TEVA was the applicant that was once eligible for 180 day exclusivity for this product. However, in a memo dated 2/28/2011 the Agency determined that TEVA forfeited eligibility for 180 day exclusivity. The '340 patent expired on 5/11/2011 so this patent is not a barrier to the approval of this ANDA. Also, since the CA against TEVA was dismissed on 5/21/2010 the '602 patent is not a barrier to approval. ANDA is eligible for Full Approval and is NOT eligible for 180 day exclusivity. Rechecked 9/24/2013- No new patents listed, no patent amendments submitted to the ANDA, no other pertinent information before the Agency. ANDA remains eligible for Full Approval.	

2. ***Labeling Endorsement***

Reviewer, : Labeling Team Leader, rlw/for:

Date_____ Date 4/2/14

REMS required? REMS acceptable?

☐Yes ☒No ☐Yes ☐No ☐n/a

Comments:

From: Grace, John F

Sent: Wednesday, April 02, 2014 9:12 AM

To: Lee, Erin; Vu, Thuyanh (Ann)

Subject: RE: Budesonide Enteric Coated Capsules ANDA 090379

concur.

From: Vu, Thuyanh (Ann)

Sent: Tuesday, April 01, 2014 4:32 PM

To: Lee, Erin; Grace, John F
Cc: Park, Chan H
Subject: RE: Budesonide Enteric Coated Capsules ANDA 090379

Erin,

There are no new RLD labeling changes, USP changes or Orange Book changes. The LBL AP SUM dated 4/17/2013 remains acceptable.

Ann

From: Grace, John F
Sent: Thursday, January 09, 2014 2:35 PM
To: Vu, Thuyanh (Ann); Lee, Erin
Subject: Re: ANDA 90379/Budesonid Caps/Barr

Concur

From: Vu, Thuyanh (Ann)
Sent: Thursday, January 09, 2014 2:00 PM
To: Lee, Erin; Grace, John F
Subject: RE: ANDA 90379/Budesonid Caps/Barr

Please endorse for me. I checked OB, Drugs@FDA, USP and DARRTS.

Thanks
Ann

From: Grace, John F
Sent: Tuesday, September 24, 2013 11:05 AM
To: Vu, Thuyanh (Ann); Lee, Erin
Subject: RE: ANDA 90379/Budesonide Cap/Barr

concur

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

From: Vu, Thuyanh (Ann)
Sent: Tuesday, September 24, 2013 10:00 AM
To: Lee, Erin; Grace, John F
Subject: RE: ANDA 90379/Budesonide Cap/Barr

Erin please sign off for me. I checked Drugs@FDA, OB and USP.

Thanks
Ann
From: Grace, John F
Sent: Wednesday, April 17, 2013 1:00 PM
To: Vu, Thuyanh (Ann); Lee, Erin
Subject: RE: ANDA 90379/budesonide cap/Barr

concur

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

From: Vu, Thuyanh (Ann)
Sent: Wednesday, April 17, 2013 1:00 PM
To: Lee, Erin; Grace, John F
Subject: RE: ANDA 90379/budesonide cap/Barr
Please endorse the AP letter for me. I checked OB, Drugs@FDA and DARRTS yesterday.

Thanks
Ann

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read — **Date 23Apr2013**
OGD Regulatory Counsel — **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 9/24/2013**
Chemistry Div. **II (Smith)** — **InitialsGJS**
Comments:CMC Acceptable.

OGD Office Management Evaluation

5. Peter Rickman — **Date 4/2/14**
Director, DLPS — **Initials rlw/for**
Para.IV Patent Cert: Yes☐ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☐
Petition: Yes☐ No☐
Entered to APTrack database ☐
GDUFA User Fee Obligation Status Met☐ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: A complete response letter issued to Barr on 4/3/12 concluding that this ANDA was acceptable for approval pending receipt by OGD of a satisfactory recommendation from CDER's Office of Compliance (OC). This recommendation was received by OGD on 4/1/14.

Bioequivalence studies (fasting and non-fasting) found acceptable for approval. In-vitro dissolution studies also found acceptable. Bio study sites have acceptable OSI inspection histories. Office-level bio endorsed 8/10/11.

Finjal-printed labeling (FPL) found acceptable for approval 4/17/13, as endorsed 4/2/14. No REMS is required.

CMC found acceptable for approval (Chemistry Review #5) 9/23/13.

OR

6. Robert L. West **Date 4/2/14**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☒ ☐ ☐ No☐
Pending Legal Action: Yes☐ ☐ No☒
Petition: Yes☐ No☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met☒ Unmet☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 4/1/14 (Verified 4/2/14). No "OAI" Alerts noted.

Barr provided a paragraph IV certification to the '602 patent and was sued within the 45-day period. The litigation was subsequently dismissed by the court with both parties entering into a settlement agreement. There are no additional patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

7. ***OGD Director Evaluation***
Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 4/2/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

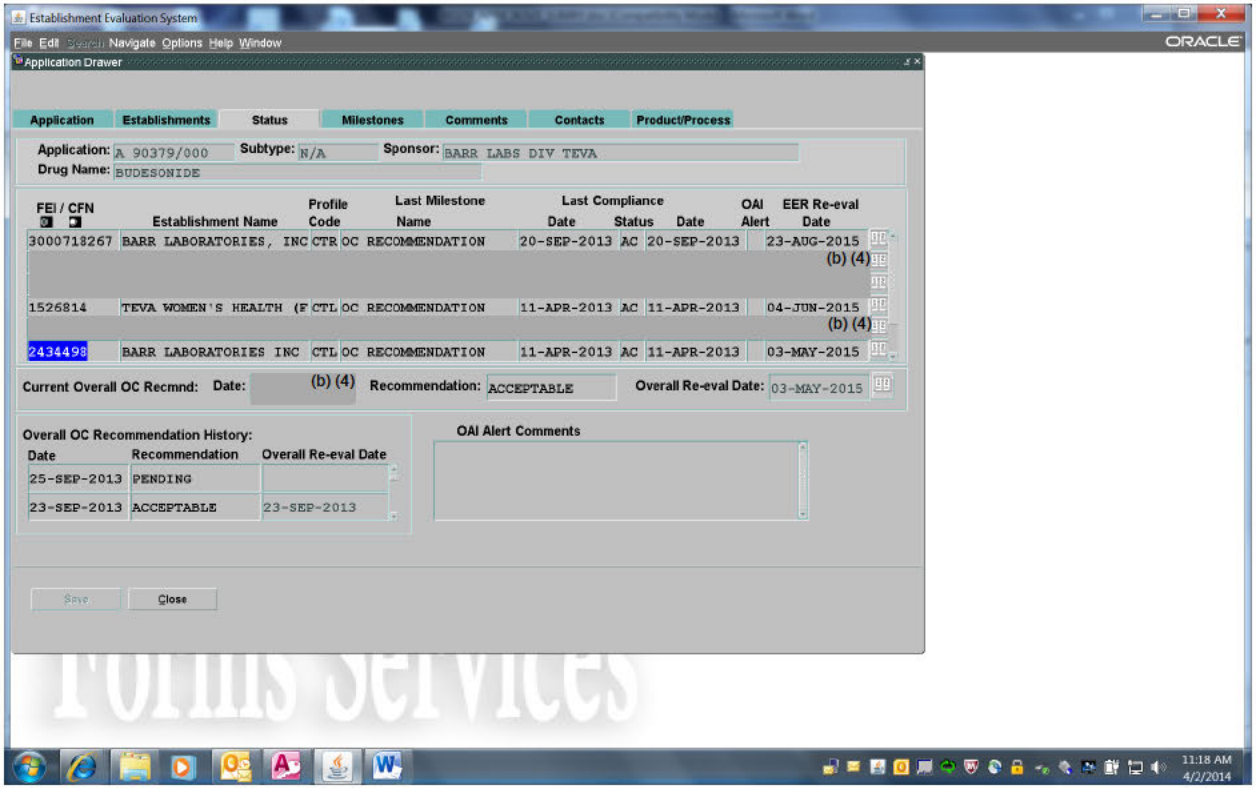
Comments:

8. Project Manager **Date 4/2/14**
☐ Office of Management, API/FDF facility list provided. **Initials EL**
Date Emailed:

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product/Process
Application: A 90379/000
Subtype: N/A
Sponsor: BARR LABS DIV TEVA
Drug Name: BUDESONIDE
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
EER Re-eval Date
3000718267 BARR LABORATORIES, INC CTR OC RECOMMENDATION 20-SEP-2013 AC 20-SEP-2013 23-AUG-2015
(b) (4)
1526814 TEVA WOMEN'S HEALTH (F CTL OC RECOMMENDATION 11-APR-2013 AC 11-APR-2013 04-JUN-2015
(b) (4)
2434498 BARR LABORATORIES INC CTL OC RECOMMENDATION 11-APR-2013 AC 11-APR-2013 03-MAY-2015
Current Overall OC Recmnd:
Date: (b) (4)
Recommendation: ACCEPTABLE
Overall Re-eval Date: 03-MAY-2015
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
25-SEP-2013 PENDING
23-SEP-2013 ACCEPTABLE 23-SEP-2013
OAI Alert Comments
Save
Close
11:18 AM
4/2/2014

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021324 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021324	001	5643602	Jul 1, 2014			U - 655	
N021324	001	5643602*PED	Jan 1, 2015				

Exclusivity Data

There is no unexpired exclusivity for this product.

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

/s/

ERIN M LEE
04/02/2014

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: BARR LABORATORIES INC TEL: 201-930-2230

ATTN: Scott Tomsky FAX: 201-489-1403

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

DATE: 2/6/2014

TO: BARR LABORATORIES INC

ATTN: Scott Tomsky

E-Mail: scott.tomsky@tevapharm.com

FAX: 201-489-1403

RE: Update summary of filed and pending original ANDA(s)

Dear Sir:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

ANDA	DRUG NAME	CHEM	BIO	MICRO	LABEL	CLINICAL	FACILITY
(b) (4)							
90308	CLOZAPINE	AQ	IQ	NA	IQ	NA	AC
(b) (4)							
90526	OXYBUTYNIN CHLORIDE	AQ	AQ	NA	AQ	AQ	AC
90379	BUDESONIDE	AQ	AQ	NA	AQ	NA	PN

CHART ACRONYMS

Column Headings

ANDA - The application number for your Abbreviated New Drug Application
DRUG NAME - The official filed name of the drug associated with the ANDA number
CHEM - Product Quality Chemistry Review
BIO - Bioequivalence Review, typically including OSI, if applicable
MICRO - Microbiology Review
LABEL - Labeling Review
CLINICAL - Clinical Review
FACILITY - Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

Discipline Notations

IQ - Inadequate. This particular discipline is currently found to be inadequate.

AQ - Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.

UR - Under Review. This particular discipline is currently assigned OR under review with the discipline team.

NR -Not Reviewed. This particular discipline is either currently not under review or assigned.

NA - Not applicable. This particular discipline is not required for the approval of this ANDA.

Facility Notations

PN - Pending, i.e., one or more facilities have been inspected and are pending an outcome.

AC - All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

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

/s/

AARON W SIGLER
02/07/2014

ROUTING SHEET

☐ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☒ CGMP

Division: II	Team: 7	PM: Frank Nice

Electronic ANDA: Yes ☒ No ☐

ANDA #:90379
Firm Name:Teva Phaermaceuticals, Inc.
ANDA Name:Budesonide Capsule, Enteric Coated, 3 mg
RLD Name:Entocort EC

Electronic AP Routing Summary Located:

\\CDSNAS\OGDS11\Chemistry Division II\Team 21\Electronic AP-TA-NAcGMPSummaries\90379.NAcGMP.doc

AP/TA Letter Located:

\\CDSNAS\OGDS11\Chemistry Division II\Team 21\Final Version For DARRTS\AP TA_NAcGMP CR WD Letters\90379.NAcGMP.ltr.doc

Project Manager Evaluation: **Date: 11/15/10 Initials:** fjn

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date February 1, 2008	Date of Application January 31, 2008	Date Acceptable for Filing April 7, 2008
Patent Certification (type) PIV	Date Patent/Excl. expires 11/15/10	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☐ Acceptable ☒ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 11/15/10 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 8/10/11 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 5/15/09 Attached labeling to Letter: Yes ☒ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 11/15/10 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 2/15/11

☒ Division

☒ 1st Generic Review

☒ Bob West / Peter Rickman/Tim Ames
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☐Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 11/17/2010**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Entocort EC NDA#21-324 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☐ No ☒ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter:

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:

Comments:ANDA submitted on 2/1/2008, BOS=Entocort EC NDA 21-324, PIV to '602 and '340. ANDA ack for filing with a PIV on 2/1/2008 (LO dated 4/7/2008). Patent Amendment submitted 1/13/2009-RR from AstraZeneca in Wilmington DE signed and dated 4/14/2008, RR from Aktiebolaget Draco in Sodetalju, Sweden signed and dated 4/21/2008, notice provided via (b) (4) to AZ in Wilmington DE with notice delivered on 4/11/2008. Patent Amendment rec'd on 2/10/2009-CA 08-305 filed in the D of DE on 5/23/2008 for infringement of the '340 and '602 patents. Since suit was filed within 45 days there is a 30 month stay of approval which expired on 10/21/10.

Marty spoke with John Durstine on 11/17/2010 and asked that he provide a legal status update for the CA which was filed in the D of DE. It is noted that the 30 month stay of approval has expired so this application may be eligible for Full Approval if the court case remains pending. This application was the first submitted which also contained a PIV certification to a listed patent. That being said, this application was not TA'd within 30 months and therefore appears to have forfeited eligibility for 180 day exclusivity.

Update 12/6/2010-Patent Amendment rec'd on 12/1/2010: cover letter states that Barr entered into a settlement agreement with AstraZeneca et. al. pursuant to the terms of the agreement CA 08-305 has been dismissed without prejudice. This agreement was entered on 5/21/2010. Furthermore according to the SA Barr is enjoined until 2/15/2012 from infringing the '340 and '602 patents by marketing their product. It is noted that the '340 patent will be expired by 2/15/2012.
By virtue of being the first ANDA that was filed with a PIV this ANDA was eligible for 180 day exclusivity for this drug product. That being said, the applicant did not secure TA within 30 months of the date their ANDA was submitted. Therefore, it appears that they have forfeited eligibility for 180 day exclusivity.

Final recommendation-ANDA is eligible for Full Approval but has forfeited 180 day.

2. ***Labeling Endorsement***

Reviewer, Angela Payne:
Date11/15/10
Initialsfjn

Labeling Team Leader, John Grace:
Date11/16/10
Initialsjg

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

Final-printed labeling (FPL) found acceptable for approval 1/19/11. No REMS is required./RLWest 6/30/11.

John/Frank

The attached labeling approval summary #1 sign-off 5.15.2009 remains acceptable. There are no new changes in DARRTS, USP, or OB to the RLD labeling. One supplement remains opened for the RLD. NO REMS REQUIRED.

Angela

concur
John

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 25Feb2011**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 6/20/2011**
Chemistry Div. **II (Fang)** **InitialsGJS**
Comments:CMC Acceptable.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 6/30/11**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
Mylan's ANDA 90-410 for this drug product was approved on 5/16/11.

OGD Office Management Evaluation

6. Peter Rickman **Date_____**
Director, DLPS **Initials_____**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: CMC found acceptable for approval (Chemistry Review #4A) 6/16/11.

Final-printed labeling (FPL) found acceptable for approval 1/19/11. No REMS is required.

AND/OR

7. Robert L. West **Date 4/2/2012**
Deputy Director, OGD **Initials TWAmes for RLWest**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes☐ No☐
Petition: Yes☐ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Withhold recommendation in EES as of 26-OCT-2011, pending re-inspection. NA cGMP letter to issue in the meanwhile./twa

Barr provided paragraph IV certifications to the '602 and '340 patents. The '340 patent expired on May 15, 2011 (with pediatric exclusivity extension). Barr was sued within the 45-day period on each patent. The patent litigation

was dismissed as a result of a settlement agreement between the parties. The settlement agreement permits Barr to market this product no earlier than February 15, 2012. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

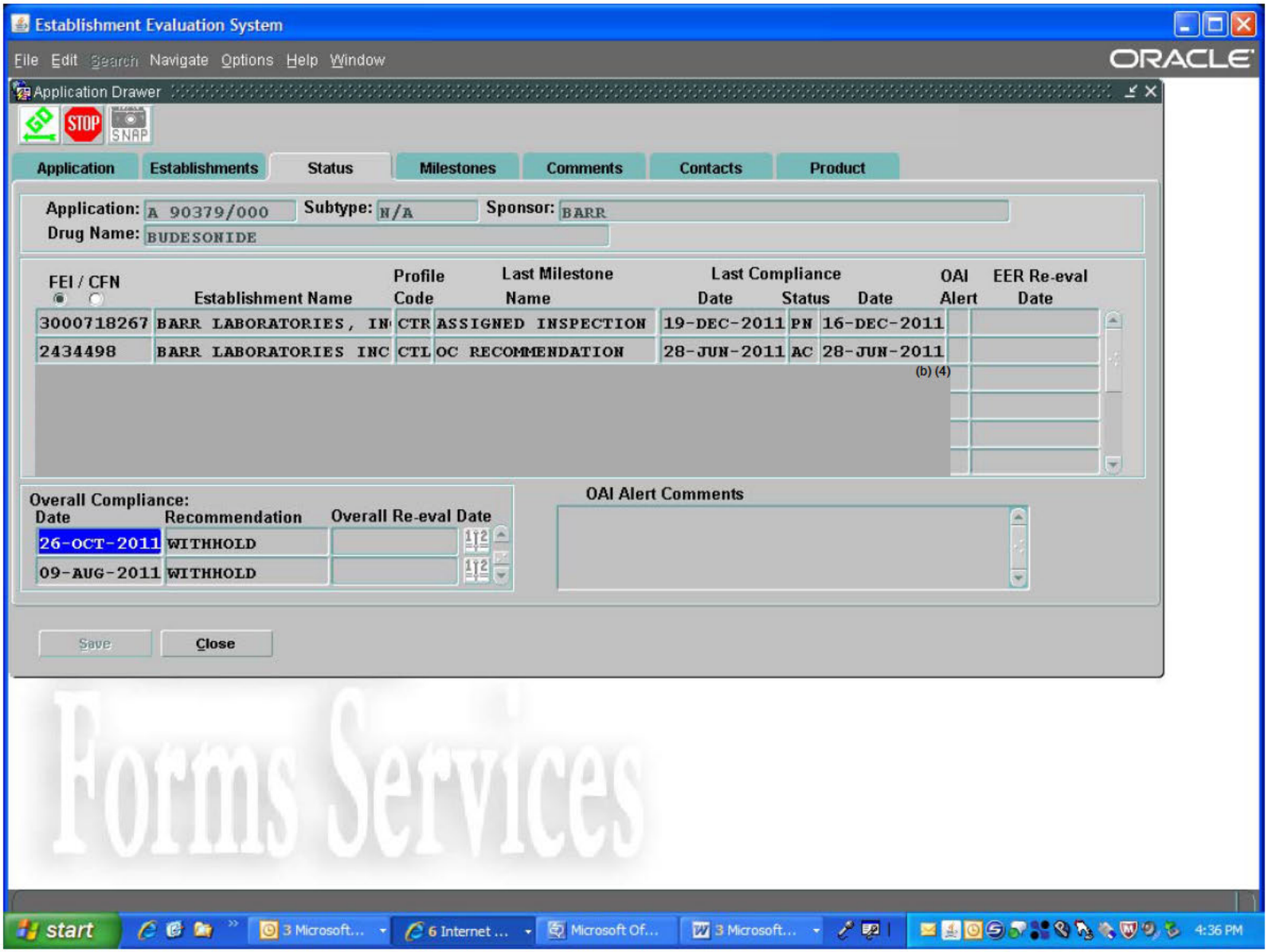
8. ***OGD Director Evaluation***
   Keith Webber
   Deputy Director, OPS
   Comments:
   First Generic Approval ☐
   PD or Clinical for BE ☐
   Special Scientific or Reg.Issue ☐
   Press Release Acceptable ☐

   Comments:

9. Project Manager
   Date 4/3/12
   Initials fjn

   Check Communication and Routing Summary into DARRTS

EER DATA:



Reference ID: 3110731

DARRTS Application History:

APPEARS THIS WAY ON ORIGINAL

Orange Book Report:

APPEARS THIS WAY ON ORIGINAL

Bio: Fasting + non-fasting, Multi-media dissolution testing reveals no "dose dumping"

ROUTING SHEET

☒ APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☒ CGMP

3/5/09

Division: II	Team: 7 (21)	PM: Frank Nice	Electronic ANDA: Yes ☒ No ☐

180 day forfeited

Mylan's ANDA 90-410 Approved 5/16/11.

ANDA #:90379
Firm Name:Teva Phaermaceuticals, Inc.
ANDA Name:Budesonide Capsule, Enteric Coated, 3 mg
RLD Name:Entocort EC

PBLOK 11/9/11, No REMS required

EES Update pending

~~EES OK 6/29/11~~

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 7\Electronic AP Summaries

OCC OK - Rev. #4A

AP/TA Letter Located:
V:\Chemistry Division II\Team 7\Final Version For DARRTS\AP TA Letters

Project Manager Evaluation: **Date: 11/15/10 Initials:** fjn

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date February 1, 2008	Date of Application January 31, 2008	Date Acceptable for Filing April 7, 2008
Patent Certification (type) PIV	Date Patent/Excl. expires 11/15/10	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ DMF#: _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☐ Acceptable ☒ OAI *EES Date Acceptable: 6/16/08* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 11/15/10 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 3/5/09 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 5/15/09 Attached labeling to Letter: Yes ☒ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 11/15/10 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☑ Regulatory Support MAB 11/17/2010 fjn 12/6/2010

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 2/25/11

☑ Division 6/20/11

☒ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

8/10/2011 Convert to NA (minor) based upon cGMPs - withhold recommendation

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

NA cGMP to issue 4/2/12

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

/s/

FRANK J NICE
04/03/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090379

Barr Laboratories, Inc.
Attention: Robert S. Vincent
Director, Regulatory Affairs
400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Budesonide Capsules (Enteric Coated), 3 mg.

Reference is also made to your amendments dated May 27 and July 26, 2011.

We have completed the review of your application and have determined that we cannot approve this application in its present form because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, or holding of Budesonide Capsules (Enteric Coated), 3 mg by Barr Laboratories, Inc. in Woodcliff Lake, NJ 07677 comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon the findings revealed during an inspection of Barr Laboratories, Inc. (Division of Teva), 2150 Perrowville Road, Forest, VA 24551-4129 conducted during the period of August 1, 2011 through August 25, 2011 by representatives of the United States Food and Drug Administration. Upon review of this report and the inspectional observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the cGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the cGMP problems, and includes a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

04/03/2012

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

TELEPHONE REQUEST

Date: July 19th, 2011
ANDA# 090379, Budesonide Capsules, 3 mg
Firm: Barr Laboratories, Inc.
Contact: Paresh Gupta @ (201) 930-3626
Reviewer: Haritha Mandula

For both your fasting (Study # 10716217) and fed studies (Study # 10716218), Please provide peak area for the drug, peak area for the internal standard, the ratio of the peak area for the drug to the peak area for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed sample for all subjects, calibration standard concentration samples, and quality control samples.

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

/s/

NAM J CHUN
07/25/2011

TELEPHONE REQUEST

Date: July 19th, 2011
ANDA# 090379, Budesonide Capsules, 3 mg
Firm: Barr Laboratories, Inc.
Contact: Nicholas Tantillo, Sr. Director, Regulatory Affairs @ (201) 930-3650
Reviewer: Haritha Mandula
Re: 20% Chromatograms

For both your fasting study (Study # 10716217), you submitted 10% of the chromatograms and for your fed study (Study # 10716218), you submitted 13% chromatograms. Please provide chromatograms for at least 20% of the subjects analyzed for both the fasting and fed studies.

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

/s/

NAM J CHUN
07/20/2011

Record of Telephone Conversation

On May 23. 2011 a T-con was made to Robert S. Vincent regarding ANDA 90-379 and their response to the Agency's information request (3/14/11) submitted 3/28/11.

The following was relayed to Robert:

(b) (4)

[redacted]

Robert Vincent acknowledged these items and agreed to get back to us regarding these issues.

Date:
5/23/11

ANDA Number:
90-379

Product Name:
Budesonide Enteric Coated Capsules, 3 mg

Firm Name:
Teva
(formerly Barr)

Firm Representative:
Robert Vincent

Phone Number:
201-930-3610

FDA Representative:
Karen Bernard, PhD
Frank Nice

Signatures:
Karen Bernard
Frank Nice PharmD

CC: ANDA 90-379

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

/s/

KAREN A BERNARD
05/24/2011

FRANK J NICE
05/24/2011

ANDA: 90379

APPLICANT: Teva Pharmaceuticals USA, Inc.

DRUG PRODUCT: Budesonide Enteric Coated Capsules, 3 mg

The comments presented below represent an Information Request.

Reference is made to your quality amendments dated April 23, 2010, October 28, 2010, and November 8, 2010.

1. (b) (4)

2. Please provide samples of all 4 batches and a sample of the RLD product to:

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855
ATTN: Dr. Frank J. Nice, RPh, DPA, CPHP

Any additional studies or data supporting (b) (4) (b) (4) should also be submitted.

We will be in communication with you upon completion of our review of the above information and data.

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

/s/

KAREN A BERNARD
03/15/2011

FRANK J NICE
03/15/2011
IR faxed to Firm on 3/14/11

RADHIKA RAJAGOPALAN
03/15/2011
For Florence Fang,

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 28, 2011

FROM: Martin Shimer
Branch Chief, Regulatory Support Branch, Office of Generic Drugs (HFD-600)

TO: ANDA 090379

SUBJECT: 180-day Exclusivity for Teva's Budesonide Enteric Coated Capsules, 3 mg

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) describes, among other things, certain events which can result in the forfeiture of a first applicant's 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv).

The forfeiture provisions of the MMA now appear at section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act). Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

> FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

A "first applicant" is eligible for 180-day exclusivity by virtue of filing a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is received. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

"Tentative approval" means, generally, that an ANDA otherwise meets the requirements for approval under the Act, but cannot be fully approved for marketing because of patent or exclusivity protections. Section 505(j)(5)(B)(iv)(II)(dd). The "failure to obtain tentative approval" forfeiture provision establishes a bright line standard: If within 30 months an ANDA has been determined by the agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant maintains eligibility for 180-day exclusivity. If this standard is not met in 30 months, eligibility for 180-day exclusivity is forfeited. It should be noted that the 30-month timeframe generally is without regard to the length of time the ANDA was under review by the Agency. One exception to this general rule, described in section 505(j)(5)(D)(i)(IV), states that forfeiture will not occur if "the failure [to obtain a tentative approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed". A second exception is found in new section 505(q)(1)(G) of the Act, enacted as part of the Food and Drug Administration Amendments Act of 2007 (Pub. Law 110-85). This provides that

> If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition,

> the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

Thus, pursuant to this provision, the 30-month period will be extended for the prescribed period during the review of a related petition subject to section 505(q).

The terms of section 505(q)(1)(G) also clarify the scope of section 505(j)(5)(D)(i)(IV). A number of comments have suggested that this section applies only when an ANDA is eligible for a tentative approval, not when an ANDA would be eligible for a final approval because there is no patent, 30-month stay or exclusivity blocking approval. Although a narrow interpretation of the scope finds support in the text of section 505(j)(5)(D)(i)(IV), the terms of section 505(q)(1)(G) clearly describe a broader scope. Section 505(q)(1)(G) expressly states that if "approval" of the first applicant's application was delayed because of a petition, the 30-month period will be extended. Thus, Congress contemplated that section 505(j)(5)(D)(i)(IV) establishes a 30-month period within which an ANDA generally must obtain either tentative approval or final approval. This interpretation squares both with the statutory language and with not permitting the 180-day exclusivity for a first applicant whose ANDA is technically deficient to delay approval of subsequent applications. Therefore, FDA interprets section 505(j)(5)(D)(i)(IV) as requiring that, unless the period is extended for one of the reasons described in the Act, a first applicant that fails to obtain either tentative approval or approval for its ANDA within 30 months it will forfeit eligibility for 180-day exclusivity.

The following is a timeline of ANDA 090379:

2/1/2008	ANDA filed
7/25/2008	Bioequivalence review (dissolution – deficient)
7/29/2008	Bioequivalence deficiencies faxed
8/25/2008	Chemistry review #1 (deficient); chemistry deficiencies faxed
1/13/2009	Patent amendment
2/10/2009	Bioequivalence amendment; patent amendment
3/5/2009	Bioequivalence review (acceptable)
3/12/2009	Labeling review (deficient); labeling deficiencies faxed
4/2/2009	Chemistry amendment
4/30/2009	Labeling amendment
5/15/2009	Labeling review (acceptable)
9/15/2009	Chemistry t-con deficiencies
9/23/2009	Chemistry amendment
11/3/2009	Chemistry amendment
12/7/2009	Chemistry review #2 (deficient); chemistry deficiencies faxed
4/27/2010	Chemistry amendment
8/1/2010	2/1/2008 plus 30 months
8/9/2010	Chemistry review #3 (deficient); chemistry deficiencies faxed
10/29/2010	Chemistry amendment
11/09/2010	Chemistry amendment
11/15/2010	Chemistry review #4 (acceptable)
12/1/2010	Patent amendment

Teva's ANDA 090379 was received on February 1, 2008, and the ANDA has not been tentatively approved. The filing date plus 30 months was August 1, 2010; therefore, Teva's ANDA was not tentatively approved within 30 months. Teva does not claim that the agency changed or reviewed the requirements for approval of Budesonide Enteric Coated Capsules, 3 mg. The agency does not find that this failure to obtain tentative approval in 30 months was caused by a change in or a review of the requirements for approval. We therefore conclude that the 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act was forfeited by Teva.

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

/s/

MARTIN H Shimer
02/28/2011

QUALITY DEFICIENCY - MINOR

ANDA 090379

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: TEVA Phamaceuticals USA TEL: 201-930-3650

ATTN: Nicholas Tantillo FAX: 201-930-3318

FROM: Frank J. Nice FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 31, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Enteric Coated (Delayed-Release) Capsules, 3 mg.

Reference is also made to your amendment dated April 23, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

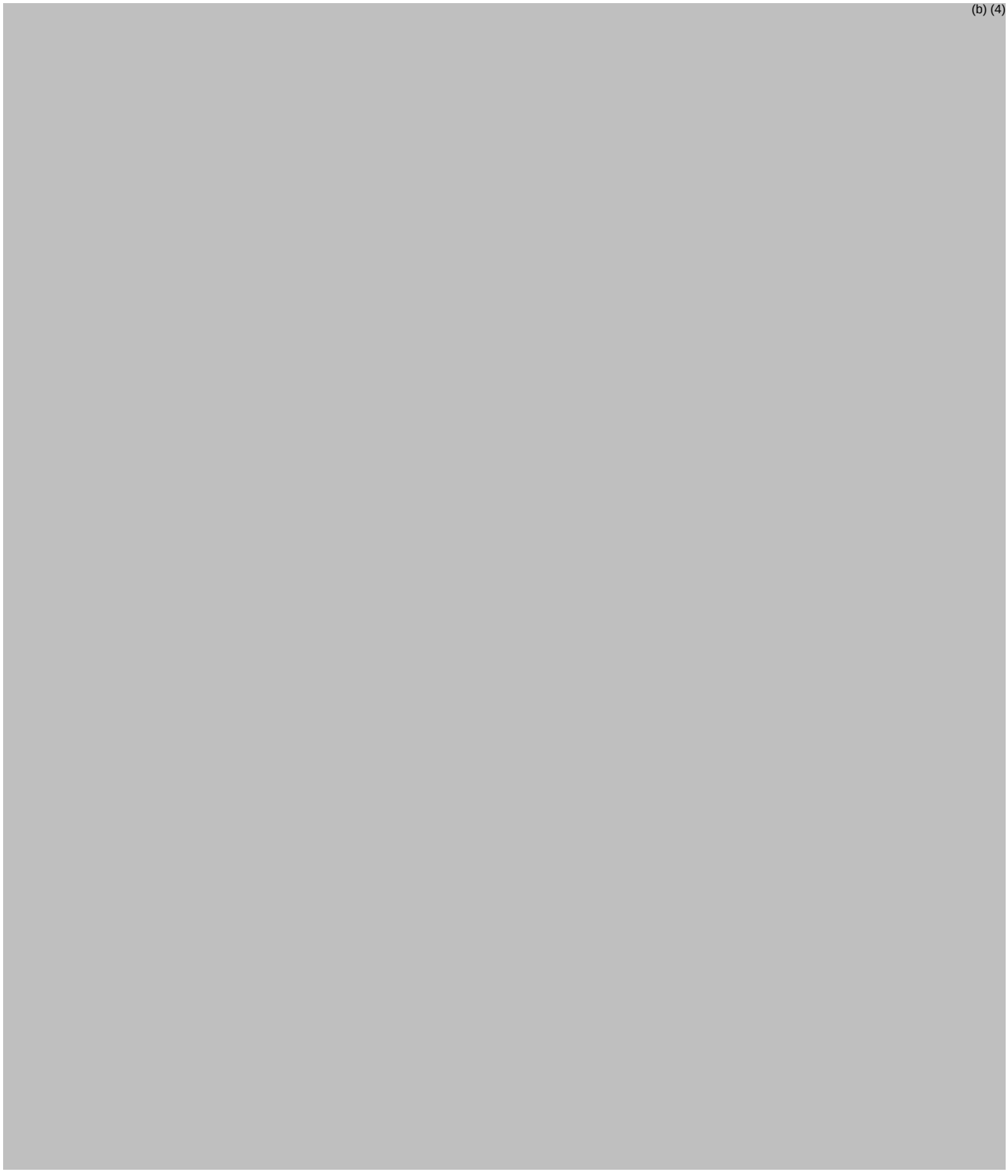
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

ANDA: 90379
APPLICANT: Teva Pharamceuticals, Inc.
DRUG PRODUCT: Budesonide Enteric-Coated (Delayed-Release) Capsules, 3 mg

The deficiencies presented below represent MINOR deficiencies.

(b) (4)



6.

7.

(b) (4)

8. For ease of review, it is also recommended that you submit a copy of your amendment response in MS Word.

Sincerely yours,

{See appended electronic signature}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90379	ORIG-1	BARR LABORATORIES INC	BUDESONIDE

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

/s/

RADHIKA RAJAGOPALAN
08/09/2010
For Florence Fang

QUALITY DEFICIENCY - MINOR

ANDA 090379

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Barr Laboratories, Inc. TEL: 201-930-2230

ATTN: Patricia Jaworski, Director, Regulatory Affairs FAX: 201-489-1403

FROM: Theresa Liu FDA CONTACT PHONE: (240) 276-8555

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated January 31, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Capsules, 3 mg.

Reference is also made to your amendment dated April 1, September 22, and November 2, 2009.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

ANDA: 090379
APPLICANT: Barr Laboratories, Inc.
DRUG PRODUCT: Budesonide Enteric-Coated Capsules (Delayed Release), 3 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

3.

4.

5.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90379	ORIG-1	BARR LABORATORIES INC	BUDESONIDE

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

/s/

DAMARIS C MALDONADO
12/07/2009

Record of Telephone Conversation

On 9/15/09 A T-con was made to Nick Tantillo at Barr. After review of the firm's April 1, 2009 amendment, the following items were requested from the firm:

(b) (4)

[redacted]

Nick Tantillo acknowledged these items and agreed to submit the requested data.

Date:
9/15/09

ANDA Number:
90-379

Product Name:
Budesonide Enteric Coated Capsules

Firm Name:
Barr

Firm Representative:
Nicholas Tantillo

Phone Number:
201-930-3650

FDA Representative:
Karen Bernard, PhD

Signatures:
Karen Bernard

CC: ANDA 90-379

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90379	ORIG-1	BARR LABORATORIES INC	BUDESONIDE
ANDA-90379	ORIG-1	BARR LABORATORIES INC	BUDESONIDE

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

/s/

KAREN A BERNARD
09/21/2009

Telephone Fax

ANDA 90-379

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
Angela.payne@fda.hhs.gov

TO: Barr Labs

TEL: 201-930-3650

ATTN: Nicholas Tantillo

FAX: 201-930-3318

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Capsules Enteric Coated.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

See attached labeling comments.

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-379 Date of Submission: 31 Jan 2008

Applicant's Name: Barr Laboratories

Established Name: Budesonide Capsules 3 mg, Enteric Coated

Labeling Deficiencies:

1. **CONTAINER** (b) (4) 100s): (b) (4) Revise (b) (4) to read "package insert". Place "enteric coated" lower on the main panel.

2. **INSERT:** Where "Entocort EC" is used in the labeling of the reference listed drug, please use "budesonide capsules (enteric coated)". Using this designation is important since the labeling also talks about uncoated oral formulation of budesonide with another product results in significant cortisol suppression. In addition, specify the source of lactose in the Description section.

3. **PATIENT LEAFLET-** See comment under insert. Also, In accordance with the requirements for a toll-free number for the reporting of adverse events, we encourage you to include the following text at the end of the Patient Information:

   Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Revise your lables and labeling, as instructed above, and submit final printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your previous submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

John Grace
3/12/2009 06:41:01 PM
for Wm Peter Rickman

COMPLETE RESPONSE -- MINOR

ANDA 90-379

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Barr Laboratories, Inc. TEL: (201) 930-3650

ATTN: Nicholas Tantillo FAX: (201) 930-3318

FROM: Theresa Liu FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated January 31, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Capsules, 3 mg.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format and MS word where applicable.
This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__**4**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

ANDA: 90-379
APPLICANT: Barr Laboratories, Inc.
DRUG PRODUCT: Budesonide Enteric-Coated Capsules (Delayed Release), 3 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

3.

4.

5.

6.

7.

Following this page, 1 Page Withheld in Full as (b)(4)

18. (b) (4)

19.

20.

21.

22.

23.

24.

25. The label storage conditions should read: “Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Sincerely yours,

{electronic signature on file}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Damaris Maldonado
8/25/2008 10:02:09 AM

BIOEQUIVALENCY AMENDMENT

ANDA 90-379

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Barr Laboratories, Inc. TEL: (201) 930-3650

ATTN: Nicholas Tantillo FAX: (201) 930-3318

FROM: Aaron Sigler FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on January 31, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Capsules, 3 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-379

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Budesonide Enteric Coated Capsule, 3 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. You stated that you used **0.01 N HCl** as the acid stage dissolution medium in the in vitro - in vivo correlation study report in the fasting study Clinical Study Report (Module 5.3.1.3, page # 660) and in the Summary Table for In vitro Dissolution Studies. But in the same in vitro - in vivo correlation study report (Module 5.3.1.3, page # 665) and in the analytical method validation report (located in Module 3.2, page # 221) you stated that **0.1N** HCl was used as the acid stage dissolution medium. Please clarify which medium, 0.1 N or 0.01 N HCl, was used in the acid stage dissolution study.

2. You conducted dissolution testing in pH 4.5 and pH 6.8 media. Please clarify the type of buffers (acetate or phosphate) used for the two dissolution media.

3. The DBE agrees that the dissolution testing should be conducted using the two-staged dissolution method as proposed by you:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature:** 37°C		**Volume**
First 2 hours;	Acid stage	0.1 N HCl or 0.01 N HCl, pending clarification	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4 and 6 hours		

However, the DBE finds your proposed buffer stage dissolution specifications of 1 hr: [redacted]%; 2 hrs: [redacted]%; 4 hrs: [redacted]%; and 6 hrs: NLT [redacted]% for your test product as too broad. Based on the dissolution testing data submitted by you, the DBE is recommending the following dissolution specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT [redacted]%

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	[redacted]%
2	[redacted]%
4	[redacted]%
6	NLT [redacted]%

Please acknowledge that you will conduct the dissolution testing for the test product using the above dissolution method and the FDA-recommended specifications.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Dale Conner

7/29/2008 05:06:49 PM

From: Shimer, Martin
Sent: Tuesday, April 29, 2008 6:12 AM
To: 'Ahmed, Sharif'
Cc: Shimer, Martin
Subject: RE: Authorization to use alternate means of providing notice for ANDA 90-379

Sharif,

It is permissible to use [redacted] (b) (4) in lieu of the US Postal Service for the purpose of providing notice to the NDA holder and any patent assignees associated with PIV certifications contained within ANDA 90-379.

Regards,

Marty

From: Ahmed, Sharif [mailto:Sharif.Ahmed@barrlabs.com]
Sent: Monday, April 28, 2008 4:49 PM
To: Shimer, Martin
Subject: Authorization to use alternate means of providing notice for ANDA 90-379

Marty,

We received a letter from OGD acknowledging receipt of Barr Laboratories, Inc. ANDA 90-379 for Budesonide Enteric Coated Capsules, 3 mg on April 7, 2008. The ANDA contained a Paragraph IV patent certification. we are requesting authorization to use a courier service such as [redacted] (b) (4) in addition to the U.S. Postal Service to provide the notice letters.

Regards,

Sharif Ahmed
Barr Laboratories, Inc.

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

/s/

Martin Shimer
5/27/2008 08:02:22 AM
CSO

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 90-379 **FIRM NAME**: BARR LABORATORIES INC.

PIV: YES **Electronic or Paper Submission:** ECTD FORMAT (ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? YES PER MARTY

3/14/08 ANY DETAILS SEE MARTY

DRUG NAME: BUDESONIDE ENTERIC COATED

DOSAGE FORM: CAPSULES, 3 MG

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

Random Queue: 7

Chem Team Leader: Darmaris Maldonado PM: Theresa Liu Labeling Reviewer: Koung Lee

Letter Date: JANUARY 31, 2008 **Received Date**: FEBRUARY 01, 2008

Comments: EC- 1 YES **On Cards:** YES

Therapeutic Code: 8015651 ULCERATIVE COLITIS

Archival copy: ECTD FORMAT **Sections** I

Review copy: E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Susan E. Pellock **Date April 4, 2008**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Nicholas Tantillo
201.930.3650 (P)
201.930.3318 (F)

First Generic: DBE Found Studies meet statutory requirements – 1st Generic Checklist is in DFS

Lot Numbers:
T: 800206
R: NC0077

FDA Form 3674 is provided in Volume 1.1

You can now access ANDA 90-379 Barr's Budesonide EC Caps DR Pellets 3 mg by using the link below.

(b) (4)

Firm was contacted on April 4, 2008 and the following information was requested:

- Please include a contact name for the testing site facilities, (b) (4)
- Please do not leave any sections blank – Unable to locate 3.2.R.1.P.2 Information on Components and 3.2.R.2.P Comparability Protocols if the sections do not apply to the ANDA please state as such

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 90-379 **FIRM NAME:** Barr Laboratories, Inc.

DRUG NAME Budesonide

DOSAGE FORM Capsules (Enteric Coated), 3 mg.
SUBJ: Request for examination of: if Budesonide product satisfies the statutory requirements of "completeness"

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____Om Anand_____ Date: ___03/26/2008_____

Reviewer

_____Paul Seo Ph.D_____ Date: ___03/26/2008_____

Team Leader

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒

1.2	**Cover Letter** Dated: JANUARY 31, 2008	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)** Baltimore, Cincinnati and NY	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES – One form for Fed (10716218) and Fasting (10716217) or Disclosure Statement (Form FDA 3455)	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ '602 exp. 1/1/2015 and '340 exp. 5/15/2011 (Statement of Notification) ☒ 3. Expiration of Patent(s): 1-01-2015 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient (b) (4) b. Type III DMF authorization letter(s) (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) No US Agent	☒
1.12.11	**Basis for Submission** NDA# : 21-324 Ref Listed Drug: ENTOCORT EC Firm: ASTRA ZENECA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Budesonide 3. Inactive ingredients 4. Route of administration Oral 5. Dosage Form Capsules 6. Strength 3 mg	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (E-Submissions) – Module 2 Intro states SPL sent** **1.14.1.1** 4 copies of draft (each strength and container) x **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained x **1.14.1.3** 1 package insert (content of labeling) submitted electronically PDF/Word ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.) (b) (4) **100s**	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained x **1.14.3.3** 1 RLD label and 1 RLD container label x	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** x **Word Processed e.g., MS Word** x A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** x **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** x **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P Drug Product** x **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **– ok as per DBE (see 1st Generic checklist in DFS)** **E-Submission: PDF** x **Word Processed e.g., MS Word** x **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (Includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers 2. Manufacturing Responsibilities 3. Type II DMF number for API 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) x **3.2.S.4.2 Analytical Procedures** x **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples x 2. Samples-Statement of Availability and Identification of: a. Drug Substance b. Same lot number(s) Barr: 0001001253 / Manuf. 21100M2 0020530 Sufficient samples of the drug substance and reference standard have been reserved for FDA testing. Samples will be submitted upon notification from the Agency to do so. **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) x 2. Applicant certificate of analysis x **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition 2) Inactive ingredients are appropriate per IIG Justified as per IIG and control document and COMIS please see below	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES 3. Function or Responsibility x 4. CFN or FEI numbers x **3.2.P.3.2 Batch Formula** Batch Formulation x **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) capsules (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization 4. Reprocessing Statement x **3.2.P.3.4 Controls of Critical Steps and Intermediates - x** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified x **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) x 2. Suppliers' COA (specifications and test results) x **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA x	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** x **3.2.P.5.2 Analytical Procedures** x **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form x 2. Same lot numbers x - Coated Intermediate Lot #800200 **Samples** **1. Finished Dosage Form** Samples will be submitted upon notification from the Agency to do so. **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form x **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data x 3. Packaging Configuration and Sizes (b) (4) 225cc/45mm 4. Container/Closure Testing x 5. Source of supply and suppliers address x	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted x 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments x **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data x 2. Batch numbers on stability records the same as the test batch **x**	☒

Finished Dosage Form	Barr Lot #	Manufacturer
Budesonide Enteric Coated Capsules, 3 mg	800206	Barr Laboratories, Inc.

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1 Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation See Below Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2 Information on Components** **3.2.R.2.P Comparability Protocols** **3.2.R.3.P Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

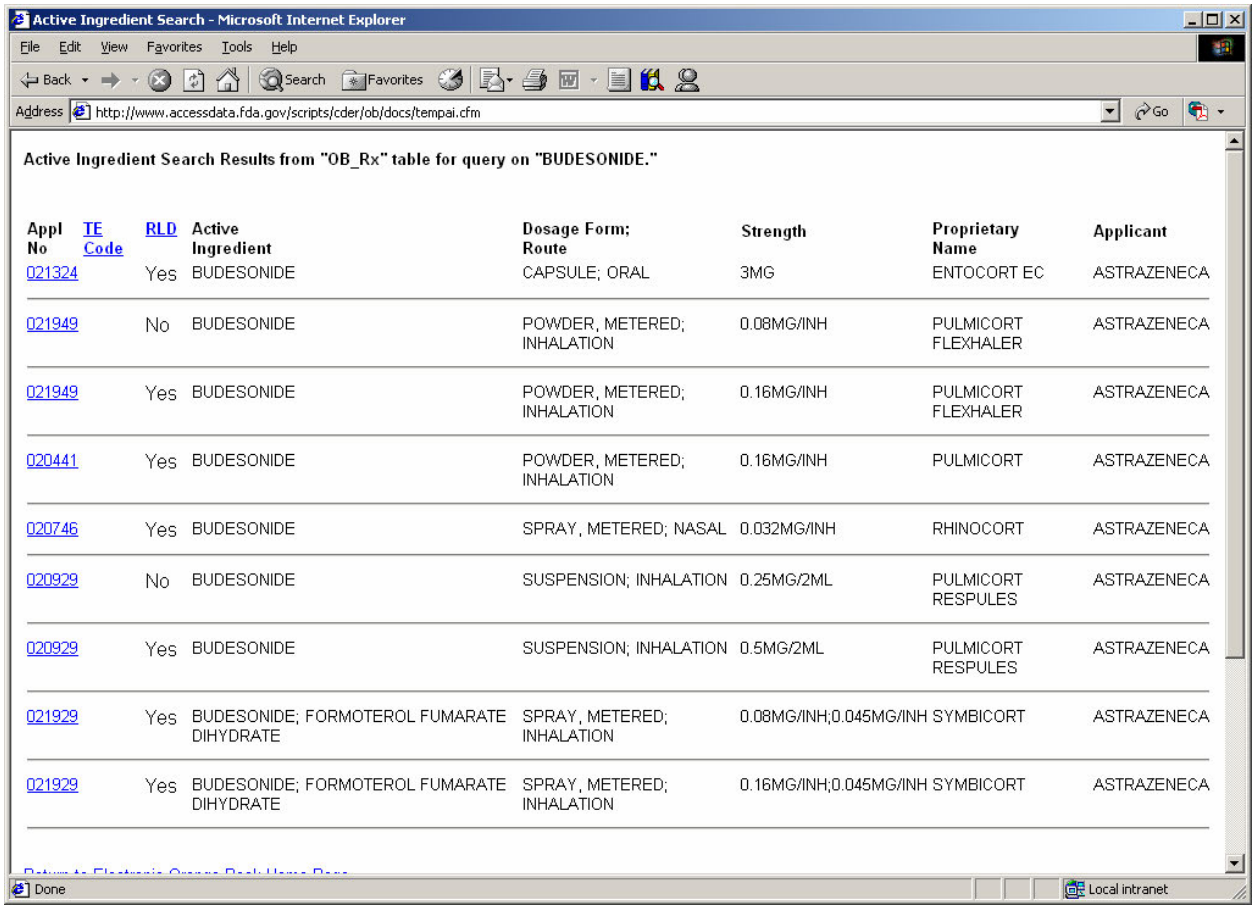
CLINICAL STUDY REPORTS – SAS / Please see 1st Generic Checklist in DFS – DBE found studies meet statutory requirements

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies** **E-Submission: PDF** **Word Processed e.g., MS Word**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type:** (Continue with the appropriate study type box below)	☐

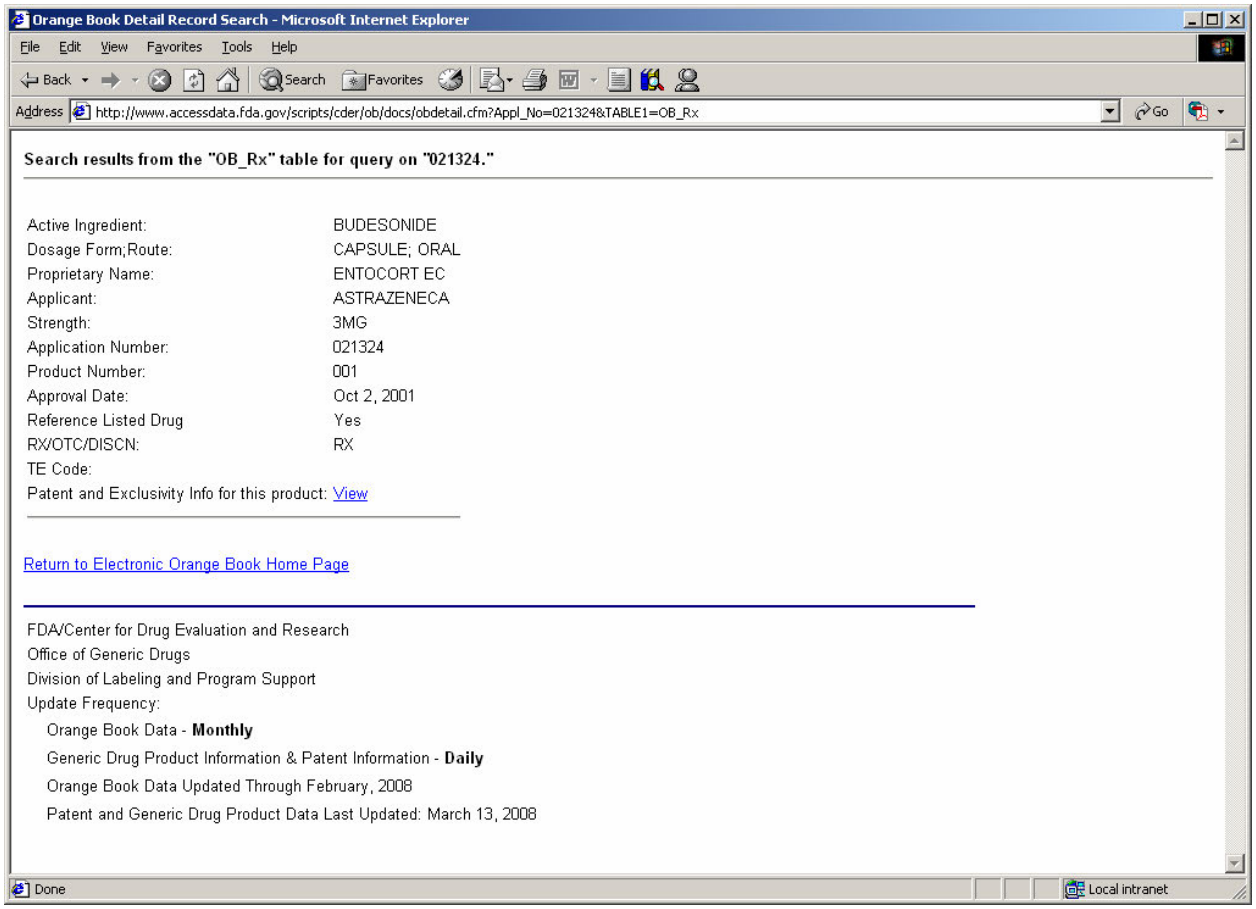
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3 In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7 Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 3 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

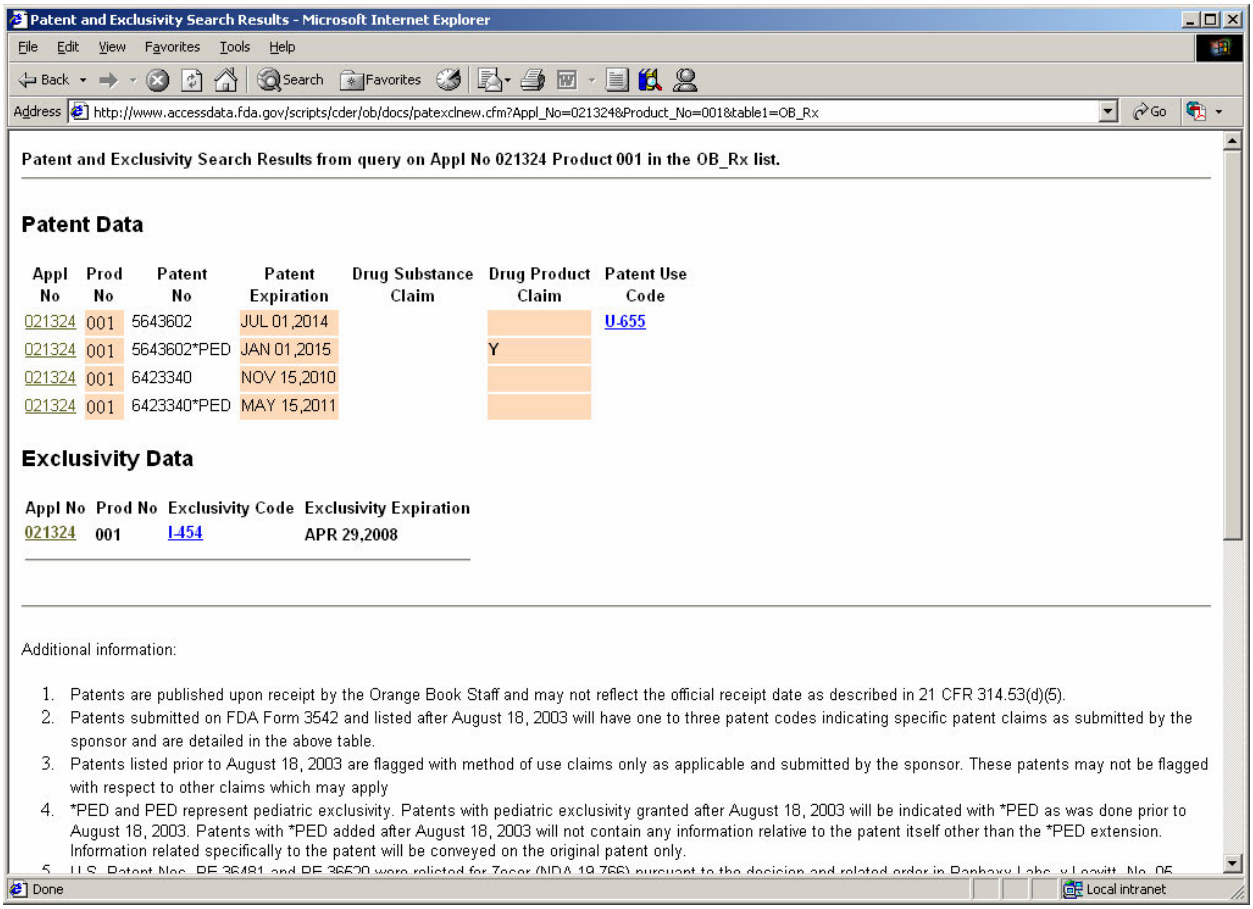
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐



Active Ingredient Search Results from "OB_Rx" table for query on "BUDESONIDE."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021324		Yes	BUDESONIDE	CAPSULE; ORAL	3MG	ENTOCORT EC	ASTRAZENECA
021949		No	BUDESONIDE	POWDER, METERED; INHALATION	0.08MG/INH	PULMICORT FLEXHALER	ASTRAZENECA
021949		Yes	BUDESONIDE	POWDER, METERED; INHALATION	0.16MG/INH	PULMICORT FLEXHALER	ASTRAZENECA
020441		Yes	BUDESONIDE	POWDER, METERED; INHALATION	0.16MG/INH	PULMICORT	ASTRAZENECA
020746		Yes	BUDESONIDE	SPRAY, METERED; NASAL	0.032MG/INH	RHINOCORT	ASTRAZENECA
020929		No	BUDESONIDE	SUSPENSION; INHALATION	0.25MG/2ML	PULMICORT RESPULES	ASTRAZENECA
020929		Yes	BUDESONIDE	SUSPENSION; INHALATION	0.5MG/2ML	PULMICORT RESPULES	ASTRAZENECA
021929		Yes	BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE	SPRAY, METERED; INHALATION	0.08MG/INH;0.045MG/INH	SYMBICORT	ASTRAZENECA
021929		Yes	BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE	SPRAY, METERED; INHALATION	0.16MG/INH;0.045MG/INH	SYMBICORT	ASTRAZENECA


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021324&TABLE1=OB_Rx
Go
Search results from the "OB_Rx" table for query on "021324."
Active Ingredient: BUDESONIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: ENTOCORT EC
Applicant: ASTRAZENECA
Strength: 3MG
Application Number: 021324
Product Number: 001
Approval Date: Oct 2, 2001
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through February, 2008
Patent and Generic Drug Product Data Last Updated: March 13, 2008
Done
Local intranet



Following this page, 10 Pages Withheld in Full as (b)(4)

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

/s/

Martin Shimer

4/7/2008 11:20:54 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-379

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
223 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated April 4, 2008.

NAME OF DRUG: Budesonide Enteric Coated Capsules, 3 mg

DATE OF APPLICATION: January 31, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 1, 2008

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8420.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Theresa Liu
Project Manager
240-276-8555

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
4/7/2008 11:20:35 AM
Signing for Wm Peter Rickman

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 90-379 **FIRM NAME:** Barr Laboratories, Inc.

DRUG NAME Budesonide

DOSAGE FORM Capsules (Enteric Coated), 3 mg.
SUBJ: Request for examination of: if Budesonide product satisfies the statutory requirements of "completeness"

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____Om Anand_____ Date: ___03/26/2008_____

Reviewer

_____Paul Seo Ph.D_____ Date: ___03/26/2008_____

Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐	02	02	Fasting protocol: eCTD m5-3-1-2, (page # 49, Report #10716217) Fed protocol: eCTD m5-3-1-2, (page # 49, Report #10716218)
Assay Methodology	☒	☐	01	01	eCTD m5-3-1-4, (page # 703, Report #10716217)(Same Analysis site for Fasting and Fed)
Procedure SOP	☒	☐			Firm submitted SOPs in section eCTD m5-3-1-4, PK repeat analysis SOP was also submitted (page # 637, Report #10716218)
Methods Validation	☒	☐	02	02	Fasting: eCTD m5-3-1-4 (page # 1041, Report #10716217) Fed : eCTD m5-3-1-4 (page # 551, Report #10716218). Also in m3.2.R.3.P – 1 and m3.2.R.3.S - 1
Study Results Ln/Lin	☒	☐	02	02	Fasting: eCTD m5-3-1-2, page # 45 Fed : eCTD m5-3-1-2, page # 45
Adverse Events	☒	☐	02	02	Fasting: eCTD m5-3-1-2, page # 40 Fed : eCTD m5-3-1-2, page # 40
IRB Approval	☒	☐	02	02	Fasting: eCTD m5-3-1-2, page # 49 Fed : eCTD m5-3-1-2, page # 49
Dissolution Data	☒	☐	02	01	Fasting: eCTD m5-3-1-3, (page # 660, Report #10716217) Fed: eCTD m5-3-1-3(page # 400, Report #10716218)
Pre-screening of Patients	☒	☐			Fasting: eCTD m5-3-7 (page # 2035, Report #10716217) Fed: eCTD m5-3-7 (page # 991, Report #10716218)
Chromatograms	☒	☐			Fasting: eCTD m5-3-1-4(page # 1141, Report #10716217) Fed : eCTD m5-3-1-4(page # 651, Report #10716218)
Consent Forms	☒	☐			Fasting: eCTD m5-3-1-2 (page # 79, Report #10716217) Fed : eCTD m5-3-1-2(page # 79, Report #10716218)

Composition	☒	☐			eCTD m2-3, page # 25
Summary of Study	☒	☐	02	02	eCTD m2-7-1 (Fasting and Fed)
Individual Data & Graphs, Linear & Ln	☒	☐	01	02	Fasting: eCTD m5-3-1-2 (page # 568, Report #10716217) Fed : eCTD m5-3-1-2(page # 179, Report #10716218)
PK/PD Data Disk Submitted)	☒	☐	02	02	eCTD m5, SAS files.
Randomization Schedule	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 154, Report #10716217) Fed : eCTD m5-3-1-2(page # 157, Report #10716218)
Protocol Deviations	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 35, Report #10716217) Fed : eCTD m5-3-1-2(page # 35, Report #10716218)
Clinical Site	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 3, Report #10716217) Fed : eCTD m5-3-1-2(page # 3, Report #10716218)
Analytical Site	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 3, Report #10716217) Fed : eCTD m5-3-1-2(page # 3, Report #10716218)
Study Investigators	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 3, Report #10716217) Fed : eCTD m5-3-1-2(page # 3, Report #10716218)
Medical Records	☒	☐	02	02	Fasting: eCTD m5-3-7 (page #2036, Report #10716217) Fed : eCTD m5-3-7(page # 992, Report #10716218)
Clinical Raw Data	☒	☐	02	02	Fasting: eCTD m5-3-7 (page #2036, Report #10716217) Fed : eCTD m5-3-7(page # 992, Report #10716218)

Test Article Inventory	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page #138, Report #10716217) Fed : eCTD m5-3-1-2 (page # 143, Report #10716218)
BIO Batch Size	☒	☐			eCTD m3-2-p-2 (page # 24 & 46)
Assay of Active Content Drug	☒	☐			eCTD m2-3 (page # 7)
Content Uniformity	☒	☐			eCTD m5-3-1-3 (page #669, Report #10716217) and (page # 400, Report #10716218)
Date of Manufacture	☒	☐			eCTD m5-3-1-3 (page #674, Report #10716217) and (page # 396, Report #10716218)
Exp. Date of RLD	☒	☐			eCTD m5-3-1-3 (page #674, Report #10716217) and (page # 396, Report #10716218)
BioStudy Lot Numbers	☒	☐			eCTD m5-3-1-3 (page #674, Report #10716217) and (page # 396, Report #10716218)
Statistics	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 161, Report #10716217) Fed : eCTD m5-3-1-2(page #163, Report #10716218)
Summary results provided by the firm indicate studies pass BE criteria	☒	☐	02	02	Fasting: eCTD m5-3-1-2 (page # 170, Report #10716217) Fed : eCTD m5-3-1-2(page #172, Report #10716218)
Waiver requests for other strengths / supporting data	☐	☒			No waiver requested

Additional Comments regarding the ANDA: None

Enter Review Productivity and Generate Report

Completed Assignment for 90379 ID: 5111

Back to Main Menu

Reviewer: Anand, Om **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Budesonide Capsules (Enteric Coated), 3 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
5111	1/31/2008	Paragraph 4	Paragraph 4 Checklist	1	1	Edit	Delete
				Bean Total:	1		

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

/s/

Paul Seo

3/26/2008 12:36:11 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : March 14, 2008

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 90-379 for Budesonide Capsules, 3 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Barr Laboratories Inc. has submitted ANDA 90-379 for Budesonide Capsules, 3 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Barr Laboratories Inc. on January 31, 2008 for its Budesonide product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

/s/

Eda Howard
3/14/2008 02:18:00 PM
APPLICATIONS EXA