CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 078879

Name: Temozolomide Capsules
5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

Sponsor: Barr Laboratories, Inc.

Approval Date: March 1, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078879

Barr Laboratories, Inc.
Attention: Nicholas Tantillo
Sr. 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 March 19, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg.

Reference is also made to the tentative approval letter issued by this office on September 10, 2009, and your amendments dated December 22, 2009; and January 29, and February 19, 2010.

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 Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Temodar Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, respectively, of Schering Corporation (Schering). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Schering's Temodar Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg, 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. 5,260,291 (the '291 patent), is scheduled to expire on February 11, 2014 (with pediatric exclusivity added).

Your ANDA contains a paragraph IV certification to the '291 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the ‘291 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Barr Laboratories, Inc. (Barr) for infringement of the listed '291 patent. You have notified the agency that Barr complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the ‘291 patent was brought against Barr in the United States District Court for the District of Delaware [Cancer Research Technology Ltd. and Schering Corporation v. Barr Laboratories, Inc., Civil Action No. 07-cv-00457]. You have also notified the agency that the court decided that the '291 patent is unenforceable; therefore, under section 505(j)(5)(B)(iii) your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity, we note that Barr was the first applicant to submit a substantially complete ANDA for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, with a paragraph IV certification to the '291 patent. Therefore, with this approval, Barr is eligible for 180 days of generic drug exclusivity for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] 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. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence – SPL for Approved ANDA 078879".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78879	ORIG-1	BARR LABORATORIES INC	TEMOZOLOMIDE

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/s/

ROBERT L WEST
03/01/2010
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-879

Barr Laboratories Inc.
Attention: Nicholas Tantillo
Senior Director, Regulatory Affairs
223 Quaker Rd
P.O.Box 2900
Pomona, NY 10970

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 19, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg.

Reference is made to your amendments dated August 23, October 5, and December 20, 2007; February 12, March 17, March 21, March 25, April 16, June 19, August 6, and December 15, 2008; and February 6, 2009 (two amendments), June 19, and August 20, 2009.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Temodar Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg of Schering Plough Corporation, 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. 5,260,291 (the '291 patent) is scheduled to expire on February 11, 2014 (with pediatric exclusivity added).

Your ANDA contains a paragraph IV certification to the '291 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides

that approval of an ANDA shall be made effective immediately, unless an action is brought against Barr Laboratories Inc. (Barr) for infringement of the listed '291 patent. You notified the agency that Barr complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '291 patent was brought against Barr within the statutory 45-day period in the United States District Court for the District of Delaware [Cancer Research Technology Limited and Schering Corporation v. Barr Laboratories Inc., Civil Action No. 07-cv-00457].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii)[1]

   b. the date the court decides[2] that the patent is invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act) or,

   c. the listed patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices

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[1] Because information on the '291 patent was submitted to FDA before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

(cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Nitin Patel, Project Manager, at (240) 276-8548.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78879	ORIG-1	BARR LABORATORIES INC	TEMOZOLOMIDE

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
09/10/2009
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

LABELING

TEMOZOLOMIDE CAPSULES

(Pharmacist and Patient Information Sheets Attached)

Revised APRIL 2008
11001280

℞ only

BARR LABORATORIES, INC.

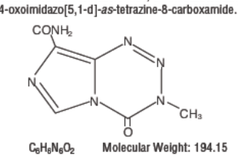
BARR LABORATORIES, INC.

℞ only

PHARMACIST: Patient Information and Pharmacist Information Sheets are attached.

DESCRIPTION

Temozolomide Capsules for oral administration contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihyd o-3-me hyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8-carboxamide. The structural formula is:



$C_6H_6N_8O_2$ Molecular Weight: 194.15

The material is a white to light tan/light pink powder. The molecule is stable at acidic pH (<5), and labile at pH >7, hence temozolomide can be administered orally. The p odrug, temozolomide, is rapidly hyd olyzed to he active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hyd olysis taking place even faster at alkaline pH.

Each capsule contains ei her 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide. The inactive ingredients for Temozolomide Capsules are anhyd ous lactose, colloidal silicon dioxide, povidone, sodium starch glycolate, stearic acid, and tartaric acid. The 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsule shells contain D&C yellow no. 10, FD&C red no. 40, FD&C yellow no. 6, gelatin, and titanium dioxide. The 140 mg capsule shell also contains D&C red no.28, FD&C blue no. 1, and FD&C green no. 3. The 180 mg capsule shell also contains FD&C blue no. 1, FD&C red no. 40, and FD&C yellow no. 6. The 5 mg imprinting ink contains ammonium hyd oxide, black i on oxide, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, and p opylene glycol. The 20 mg imprinting ink contains ammonium hyd oxide, black i on oxide, p opylene glycol, red i on oxide, shellac glaze, and yellow i on oxide. The 100 mg imprinting ink contains FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, polyvinylpyr olidone, p opylene glycol, sodium hyd oxide, and titanium dioxide. The 140 mg, 180 mg, and 250 mg 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, pharmaceutical glaze, p opylene glycol, and synthetic black i on oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to he reactive compound MTIC. The cytotoxicity of MTIC is hought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N7 positions of guanine.

Pharmacokinetics

Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (f om 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated wi h a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma p oteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination

Temozolomide is spontaneously hyd olyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is fur her hyd olyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosyn hesis and to me hylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor ole in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, he exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of he recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m².

Special Populations

Age

Population pharmacokinetic analysis indicates that age (range 19 to 78 years) has no influence on he pharmacokinetics of temozolomide. In he anaplastic ast ocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neut openia and Grade 4 h ombocytopenia in the first cycle of therapy han patients under 70 years of age (see PRECAUTIONS).

Gender

Population pharmacokinetic analysis indicates hat women have an app oximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neut openia and th ombocytopenia in the first cycle of therapy han men (see ADVERSE REACTIONS).

Race

The effect of race on he pharmacokinetics of temozolomide has not been studied.

Tobacco Use

Population pharmacokinetic analysis indicates hat he oral clearance of temozolomide is similar in smokers and nonsmokers.

Creatinine Clearance

Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m² has no effect on he clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients w th severely impaired renal function (CLcr <36 mL/min/m²). Caution should be exercised when temozolomide capsules are administered to patients w th severe renal impairment. Temozolomide has not been studied in patients on dialysis.

Hepatically Impaired Patients

In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients wi h mild-to-moderate hepatic impairment (Child's-Pugh Class I - II) were similar to those observed in patients wi h norma hepatic function. Caution should be exercised when temozolomide is administered to patients wi h severe hepatic impairment.

Drug-Drug Interactions

In a multiple-dose study, administration of temozolomide capsules with ranitidine did not change he C_{max} or AUC values for temozolomide or MTIC. Population analysis indicates hat administration of valp oic acid decreases the clearance of temozolomide by about 5% (see PRECAUTIONS).

Population analysis failed to demonstrate any influence of coadministered dexame hasone, p ochlorperazine, phenytoin, carbamazepine, ondanset on, H_2-receptor antagonists, or phenobarbital on he clearance of orally administered temozolomide.

CLINICAL STUDIES

Refractory (Anaplastic Astrocytoma)

A single-arm, multicenter study was conducted in 162 patients who had anaplastic ast ocytoma at first relapse and who had a baseline Ka nofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nit osourea wi h or wi hout o her chemotherapy. Fifty-four patients had disease p ogression on prior therapy wi h both a nit osourea and p ocarbazine and heir malignancy was considered refractory to chemo herapy (refractory anaplastic ast ocytoma population). Median age of his subg oup of 54 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of >80. Sixty- hree percent of patients had surgery o her han a biopsy at he time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a g oss total resection. Eighteen percent of patients had surgery at he time of first relapse. The median time f om initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

Temozolomide Capsules were given for he first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m²/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neut ophil count was >1.5 x 10^9/L (1,500/µL) and the nadir and Day 29, Day 1 of next cycle, platelet count was >100 x 10^9/L (100,000/µL), he temozolomide dose was increased to 200 mg/m²/day for the first 5 consecutive days of a 28-day cycle.

In he refractory anaplastic ast ocytoma population, he overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and he median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, p ogression-free survival at 6 mon hs was 45% (95% confidence interval 31% to 58%) and p ogression-free survival at 12 months was 29% (95% confidence interval 16% to 42%). Median p ogression-free survival was 4.4 months. Overall survival at 6 mon hs was 74% (95% confidence interval 62% to 86%) and 12-mon h overall survival was 65% (95% confidence interval 52% to 78%). Median overall survival was 15.9 mon hs.

INDICATIONS AND USAGE

Temozolomide Capsules are indicated for he treatment of adult patients wi h refractory anaplastic ast ocytoma, ie, patients who have experienced disease p ogression on a drug regimen containing nit osourea and p ocarbazine.

CONTRAINDICATIONS

Temozolomide Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of its components. Temozolomide is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to MTIC.

WARNINGS

Patients treated wi h temozolomide capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neut ophil count (ANC) ≥ 1.5 x 10^9/L and a platelet count ≥ 100 x 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or wi hin 48 hours of that day, and weekly until he ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x 10^9/L. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Very rare cases of myelodysplastic synd ome and secondary malignancies, including myeloid leukemia, have also been observed.

There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving ste oids, should be observed closely for he development of PCP regardless of he regimen.

Pregnancy

Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m²/day in rats and 150 mg/m²/day in rabbits during the period of organogenesis (3/8 and 3/4 he maximum recommended human dose, respectively) caused nume ous malformations of the exte nal organs, soft tissues, and skeleton in bo h species. Doses of 150 mg/m²/day in rats and rabbits also caused embryole hality as indicated by increased resorptions. There are no adequate and well-cont olled studies in pregnant women. If this drug is used during pregnancy, or if he patient becomes pregnant while taking his drug, he patient should be apprised of the potential hazard to he fetus. Women of childbearing potential should be advised to avoid becoming pregnant during herapy with temozolomide capsules.

PRECAUTIONS

Information for Patients

Nausea and vomiting were among he most frequently occurring adverse events. These were usually either self-limiting or readily cont olled with standard antiemetic herapy. Capsules should not be opened. If capsules are accidentally opened or damaged, rigo ous precautions should be taken wi h he capsule contents to avoid inhalation or contact with he skin or mucous membranes. The medication should be kept away f om children and pets.

Drug Interaction

Administration of valp oic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Patients with Severe Hepatic or Renal Impairment

Caution should be exercised when Temozolomide Capsules are administered to patients wi h severe hepatic or renal impairment (see Special Populations).

Geriatrics

Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whe her hey responded differently f om younger subjects. O her reported clinical experience has not identified differences in responses between he elderly and younger patients. Caution should be exercised when treating elderly patients.

In he anaplastic ast ocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neut openia and Grade 4 th ombocytopenia (2/8; 25%, p=0.31 and 2/10; 20%, p=0.09, respectively) in he first cycle of herapy than patients under 70 years of age (see ADVERSE REACTIONS).

Laboratory Tests

For he 28-day treatment cycles, a complete blood count should be obtained on Day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if he ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Standard carcinogenicity studies were not conducted wi h temozolomide. In rats treated wi h 200 mg/m² temozolomide (equivalent to he maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in bo h males and females. Wi h 6 cycles of treatment at 25, 50, and 125 mg/m² (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses and fib osarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and p ostate; carcinoma of he seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of he skin, lung, pituitary, and thy oid were observed at he high dose.

Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).

Rep oductive function studies have not been conducted wi h temozolomide. However, multicycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial cells/immature sperm, testicular at ophy) at doses of 50 mg/m² in rats and 125 mg/m² in dogs (1/4 and 5/8, respectively, of he maximum recommended human dose on a body surface area basis).

Pregnancy Category D

See WARNINGS section.

Nursing Mothers

It is not known whe her his drug is excreted in human milk. Because many drugs are excreted in human milk and because of he potential for serious adverse reactions in nursing infants f om temozolomide capsules, patients receiving temozolomide should discontinue nursing.

Pediatric Use

Temozolomide effectiveness in children has not been demonstrated. Temozolomide capsules have been studied in 2 open label Phase 2 studies in pediatric patients (age 3-18 years) at a dose of 160-200 mg/m² daily for 5 days every 28 days. In one trial conducted by the Schering Corporation, 29 patients wi h recurrent brain stem glioma and 34 patients wi h recurrent high grade ast ocytoma were en olled. All patients had failed surgery and radiation herapy, while 31% also failed chemotherapy. In a second Phase 2 open label study conducted by he Children's Oncology G oup (COG), 122 patients were en olled, including medulloblastoma/PNET(29), high grade ast ocytoma (23), low grade ast ocytoma (22), brain stem glioma (16), ependymoma (14), o her CNS tumors (9), and non-CNS tumors (9). The temozolomide toxicity p ofile in children is similar to adults. Table 1 shows the adverse events in 122 children in the COG Phase 2 study.

Table 1

Adverse Events Reported in Pediatric Cooperative Group Trial (≥10%)

	No. (%) of Temozolomide Patients (N=122)[a]	
Body System/Organ Class Adverse Event	All Events	Gr 3/4
Subjects Reporting an AE	**107 (88)**	**69 (57)**
Body as a Whole		
Central and Peripheral Nervous System		
Central cerebral CNS cortex	22 (18)	13 (11)
Gastrointestinal System		
Nausea	56 (46)	5 (4)
Vomiting	62 (51)	4 (3)
Platelet, Bleeding and Clotting		
Th ombocytopenia	71 (58)	31 (25)
Red Blood Cell Disorders		
Decreased Hemoglobin	62 (51)	7 (6)
White Cell and RES Disorders		
Decreased WBC	71 (58)	21 (17)
Lymphopenia	73 (60)	48 (39)
Neut openia	62 (51)	24 (20)

a) These various tumors included he following: PNET-medulloblastoma, low grade ast ocytoma, brain stem tumor, ependymoma, mixed glioma, oligodend oglioma, neu oblastoma, Ewing's sarcoma, pineoblastoma, alveolar soft part sarcoma, neurofib osarcoma, optic glioma, and osteosarcoma.

ADVERSE REACTIONS IN ADULTS

Refractory Anaplastic Astrocytoma

Tables 2 and 3 show he incidence of adverse events in he 158 patients in the anaplastic ast ocytoma study for whom data are available. In the absence of a cont ol g oup, it is not clear in many cases whe her hese events should be attributed to temozolomide or he patients' underlying conditions, but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug related. The most frequently occurring side effects were nausea, vomiting, headache, and fatigue. The adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, wi h nausea and vomiting readily cont olled wi h antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (h ombocytopenia and neut openia) was he dose-limiting adverse event. It usually occurred wi hin the first few cycles of herapy and was not cumulative.

Myelosuppression occurred late in the treatment cycle and retu ned to normal, on average, wi hin 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neut ophils (range 1 to 44 days). Only 14% (22/158) of patients had a neut ophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of he next cycle. Less han 10% of patients required hospitalization, blood transfusion, or discontinuation of herapy due to myelosuppression.

In clinical trial experience wi h 110 to 111 women and 169 to 174 men (depending on measurements), here were higher rates of Grade 4 neut openia (ANC < 500 cells/µL) and th ombocytopenia (< 20,000 cells/µL) in women han men in he first cycle of herapy (12% versus 5% and 9% versus 3%, respectively).

In he entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neut openia or h ombocytopenia in he first cycle, respectively. For patients less han or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neut openia or hrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

Table 2

Adverse Events in the Anaplastic Astrocytoma Trial in Adults (>5%)

	No. (%) of Temozolomide Patients (N=158)	
	All Events	Grade 3/4
Any Adverse Event	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
As henia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)

(over)

TEMOZOLOMIDE CAPSULES
PHARMACIST INFORMATION SHEET

IMPORTANT DISPENSING INFORMATION

For every patient, temozolomide must be dispensed in a separate vial or in its original glass bottle making sure each container lists the strength per capsule and that patients take the appropriate number of capsules from each bottle or vial.

Please see the dispensing instructions below for more information.

What is Temozolomide?

Temozolomide is an oral alkylating agent for refractory anaplastic ast ocytoma.

How is Temozolomide dosed?

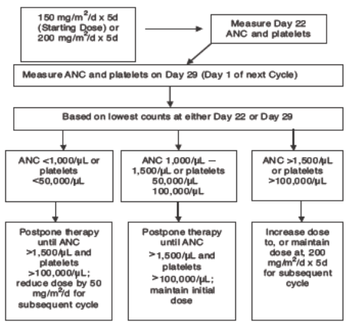
The daily dose of Temozolomide Capsules for a given patient is calculated by the physician, based on he patient's body surface area (BSA). The resulting dose is hen ounded off to the nearest 5 mg. An example of the dosing may be as follows: he initial daily dose of temozolomide in milligrams is he BSA multiplied by mg/m²/day, (a patient wi h a BSA of 1.84 is 1.84 x 75 mg = 138, or 140 mg/day). The dose for subsequent cycles may be adjusted according to nadir neut ophil and platelet counts in the previous cycle and at he time of initiating he next cycle.

How might the dose of Temozolomide be modified for Refractory Anaplastic Astrocytoma?

Dosage of temozolomide must be adjusted according to nadir neut ophil and platelet counts in the previous cycle and neut ophil and platelet counts at he time of initiating he next cycle. The initial dose is 150 mg/m² orally once daily for 5 consecutive days per 28-day treatment cycle. If bo h he nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neut ophil counts (ANC) are ≥ 1.5 x 10^9/L (1,500/µL) and bo h the nadir and Day 29, Day 1 of next cycle platelet counts are ≥ 100 x 10^9/L (100,000/µL), the temozolomide dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or wi hin 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/µL) and he platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of temozolomide should not be started until he ANC and platelet count exceed these levels. If the ANC falls to <1.0 x 10^9/L (1,000/µL) or the platelet count is <50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m², but not below 100 mg/m², he lowest recommended dose (see Table 1 below).

TABLE 1

Dosing Modification Table for Refractory Anaplastic Astrocytoma



What is the Temozolomide Capsules treatment regimen?

Temozolomide is given for 5 consecutive days on a 28-day cycle. Patients should continue taking temozolomide until heir physician determines hat their disease has p ogressed, up to 2 years, or until unacceptable side effects or toxicities occur. Physicians may alter he treatment regimen for a given patient.

How is Temozolomide taken?

Patients should take each day's dose with a full glass of water at he same time each day. Taking he medication on an empty stomach or at bedtime may help ease nausea. If patients are also taking antinausea or o her medications to relieve the side effects associated with temozolomide, hey should be advised to take hese medications 30 minutes before hey take temozolomide. Temozolomide causes he rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split he capsules. If capsules are accidentally opened or damaged, rigo ous precautions should be taken wi h he capsule contents to avoid inhalation or contact with he skin or mucous membranes. The medication should be kept away f om children and pets. The temozolomide capsules should be swallowed whole and **NEVER CHEWED.**

What should the patient avoid during treatment with Temozolomide?

There are no dietary restrictions for patients taking temozolomide. Temozolomide may affect testicular function, so male patients should exercise adequate bir h cont ol measures. Temozolomide may cause birth defects. Female patients should avoid becoming pregnant while receiving this drug. Women who are nursing prior to receiving temozolomide should discontinue nursing. It is not known whe her temozolomide is excreted into breast milk.

What are the side effects of Temozolomide?

Nausea and vomiting are the most common side effects associated wi h temozolomide. Noncumulative myelosuppression is he dose-limiting toxicity. Patients should be evaluated periodically by heir physician to monitor blood counts.

Other commonly reported side effects reported by patients taking temozolomide are fatigue, constipation, alopecia, anorexia, and headache.

How is Temozolomide supplied?

Temozolomide capsules are available in 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg strengths. The 5 mg, 20 mg, 100 mg, and 250 mg capsules contain an off-white capsule body wi h an off-white cap. The 140 mg capsules contain an off-white capsule body with a blue cap. The 180 mg capsules contain an off-white capsule body wi h a dark orange cap. Each capsule contains color-coded printing according to streng h.

Temozolomide Capsule Strength	Color
5 mg	Green Imprint
20 mg	B own Imprint
100 mg	Blue Imprint
140 mg	Blue Cap
180 mg	Dark Orange Cap
250 mg	Black Imprint

The 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsule strengths are available in 5 count and 20 count packages.

How is Temozolomide dispensed?

Each streng h of temozolomide must be dispensed in a separate vial or in its original glass bottle (one streng h per one container). Follow he instructions below:

Based on he dose prescribed, determine he number of each streng h of temozolomide capsules needed for he full 42 or 5 day cycle as prescribed by he physician. For example, in a 5 day cycle, 275 mg/day would be dispensed as five 250 mg capsules, five 20 mg capsules and five 5 mg capsules. Label each container with he app opriate number of capsules to be taken each day. Dispense to he patient, making sure each container lists the streng h (mg) per capsule and hat he or she understands to take he app opriate number of capsules of temozolomide f om each bottle or vial to equal he total daily dose prescribed by the physician.

How can Temozolomide be ordered?

Temozolomide can be ordered f om your wholesaler. It is important to understand if temozolomide is being used as part of a 42 day regimen or as part of a five-day course. Remember to order enough temozolomide for the app opriate cycle.

(over)

(cut here)

TEMOZOLOMIDE CAPSULES
PATIENT INFORMATION SHEET

PHARMACIST: Cut at line and give to patients.

IMPORTANT INFORMATION FOR THE PATIENT

What are Temozolomide Capsules?

Temozolomide Capsules are used to treat certain cance ous tumors in he brain of adult patients. Your doctor has prescribed Temozolomide Capsules as part of your cancer treatment. Temozolomide Capsules are a drug you take by mouth that interferes with cell g ow h, especially in cells hat are growing rapidly, such as cance ous cells. Temozolomide Capsules have been shown to help slow the g ow h of certain cance ous tumors. When given to patients wi h brain cancer, Temozolomide Capsules have been shown to reduce he size of he tumor in some patients.

Who should not take Temozolomide Capsules?

You should not take Temozolomide Capsules if you have had an allergic reaction to DTIC-Dome (dacarbazine), a different treatment for cancer. If you have had an allergic reaction before to drugs such as DTIC-Dome, be sure to tell your doctor before taking Temozolomide Capsules. If you are allergic to drugs similar to Temozolomide Capsules, you may also have an allergic reaction to Temozolomide Capsules.

How should I take Temozolomide Capsules?

Take each day's dose of capsules at one time, wi h a full glass of water. **DO NOT** open or split he capsules. If he capsules are accidentally opened or damaged, you should be extremely careful to avoid inhaling he powder in he capsules or getting it on your skin or mucous membranes (e.g., in nose or mou h). Flush the area wi h water if contact occurs. The medication should be kept away f om children and pets. They should be swallowed whole and **NEVER CHEWED.** If capsules are vomited do not take a second dose. New capsules should not be taken until he next planned dose. The medicine is used best by your body if you take it at the same time every day in relation to a meal. To reduce nausea, try to take Temozolomide Capsules on an empty stomach or at bedtime. Your doctor may also have prescribed antinausea or other medications to relieve he side effects associated with Temozolomide Capsules. Antinausea medications should be taken as directed by your doctor. It is important hat you continue to see your doctor regularly to check your p ogress. Your doctor can uncover side effects of treatment that you might not notice.

Because Temozolomide Capsules are a drug you take by mouth, you can take it at home. Be sure you follow the schedule that your doctor has prescribed for you. The schedule you may be prescribed is, Temozolomide Capsules taken for 5 consecutive days only, hen you must **STOP** taking Temozolomide Capsules for the next 23 days. This total period of 5 days on Temozolomide Capsules and 23 days off Temozolomide Capsules is called one treatment cycle. Your dose is based on your height and weight, and he number of treatment cycles will depend on how you respond to and tolerate his treatment.

Temozolomide Capsules come in different streng h capsules (shown on he outer label in mg). Each strength has a different color band. Depending on he dose of Temozolomide Capsules hat your doctor prescribes, you may have to take several capsules on each dosing day of a treatment cycle (Day 1 h ough Day 5, followed by 23 days wi h no capsules) or the 42 days (up to 49 days) of consecutive treatment schedule wi h radio herapy.

- Be sure you understand exactly how many capsules you need to take of each strength. Ask your doctor or pharmacist to write down the number of each streng h (include color) hat you need to take each dosing day.
- Be sure you know exactly which days are your dosing days.
- Be sure to review he dose wi h your healthcare p ovider each time you start a new cycle. Sometimes the dose or the mix of capsules you need to take will be different f om he last cycle.
- Once you take he medicine home, if you are confused or unsure about how to take your dose, contact your doctor or pharmacist immediately.

Your doctor may have prescribed a treatment regimen that is different f om those discussed in his information sheet. If so, make sure you follow the specific instructions given to you by your doctor. You should talk to your doctor about what to do if you miss a day. If you take more han the prescribed amount of medicine, contact your doctor right away. It is important that you understand your dosage regimen, it is also important hat you do not take more than he amount of Temozolomide Capsules prescribed for you. Overdoses can lead to serious outcomes including severe low blood counts and possible dea h.

How are Temozolomide Capsules supplied?

The 5 mg, 20 mg, 100 mg and 250 mg Temozolomide Capsules contain an off-white capsule body with an off-white cap. The 140 mg capsules contain an off-white capsule body wi h a blue cap. The 180 mg capsules contain an off-white capsule body with a dark orange cap. Each capsule contains color-coded printing according to strength, each a different size. The capsules are available in six different streng hs.

Temozolomide Capsule Strength	Color
5 mg	Green Imprint
20 mg	B own Imprint
100 mg	Blue Imprint
140 mg	Blue Cap
180 mg	Dark Orange Cap
250 mg	Black Imprint

What should I avoid while taking Temozolomide Capsules?

There are no limitations on what you may eat or drink while taking Temozolomide Capsules. However, to ease nausea, try to take Temozolomide Capsules on an empty stomach.

Temozolomide Capsules may cause bir h defects. Therefore, male or female patients who take Temozolomide Capsules should use effective bir h cont ol. Female patients should avoid becoming pregnant while receiving his drug. You should not breast feed an infant while taking Temozolomide Capsules. It is not known whether Temozolomide Capsules pass into breast milk. Because many drugs do pass into breast milk, here is he possibility of serious harm to nursing infants.

What are the possible or reasonably likely side effects of Temozolomide Capsules?

Nausea and vomiting are he most common side effects associated wi h Temozolomide Capsules. Your doctor can prescribe medicines that may help reduce some of these. Other common side effects include headache, feeling tired, loss of appetite, hair loss and constipation.

Temozolomide Capsules also can reduce he number of certain types of blood cells, which can have serious effects. White blood cells are needed to fight infections. Lowering of white blood cells, could result in a serious infection with a potential outcome of death. Platelets are needed in he normal course of blood clotting. Lowering of platelets does not allow your blood to clot normally, which can result in bleeding episodes. Therefore, it is important hat your doctor check your blood periodically while you are taking Temozolomide Capsules to see if these side effects are occurring. Patients age 70 or older, women, and patients who have had chemotherapy or radiation therapy may be more likely to have heir blood cells affected.

There are o her side effects associated wi h Temozolomide Capsules. They are included in a longer, more technical information leaflet written for heal hcare p oviders hat you can get f om your doctor or pharmacist.

General information about the use of prescription drug products.

Medicines are sometimes prescribed for purposes o her han hose listed in a Patient Package Insert. You should contact your heal hcare p ofessional regarding any conce ns you may have about using Temozolomide Capsules. Temozolomide Capsules should not be used for a condition for which it was not prescribed, and it should not be given to o her persons.

BARR LABORATORIES, INC.
POMONA, NY 10970

Revised APRIL 2008
PL-1075, 1076, 1077, 1078, 1159, 1160

For examples of dosing regimens, please refer to he Full Prescribing Information (Table 6).

Temozolomide Product	NDC Number
250 mg capsules (5 count)	0555-1075-52
250 mg capsules (20 count)	0555-1075-18
180 mg capsules (5 count)	0555-1160-52
180 mg capsules (20 count)	0555-1160-18
140 mg capsules (5 count)	0555-1159-52
140 mg capsules (20 count)	0555-1159-18
100 mg capsules (5 count)	0555-1076-52
100 mg capsules (20 count)	0555-1076-18
20 mg capsules (5 count)	0555-1077-52
20 mg capsules (20 count)	0555-1077-18
5 mg capsules (5 count)	0555-1078-52
5 mg capsules (20 count)	0555-1078-18

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POMONA, NY 10970

Revised APRIL 2008
PI-1075, 1076, 1077, 1078, 1159, 1160

Table 2 (continued)

Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Pares hesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diar hea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision Abnormal*	8 (5)	

*Blurred vision, visual deficit, vision changes, vision t oubles.

Table 3
Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial in Adults

	Temozolomide[a]
Hemoglobin	7/158 (4%)
Lymphopenia	83/152 (55%)
Neut ophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

[a]Change f om Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

In addition, the following spontaneous adverse experiences have been reported during he marketing surveillance of temozolomide capsules: allergic reactions, including rare cases of anaphylaxis. Rare cases of erythema multiforme have been reported which resolved after discontinuation of temozolomide and, in some cases, recurred upon rechallenge. Rare cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have also been reported.

OVERDOSAGE

Doses of 500, 750, 1,000, and 1,250 mg/m^2 (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported wi h any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multi-organ failure, and dea h. There are reports of patients who have taken more han 5 days of treatment (up to 64 days) wi h adverse events reported including bone mar ow suppression, which in some cases was severe and p olonged, and infections and resulted in death. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be p ovided as necessary.

DOSAGE AND ADMINISTRATION

Dosage of Temozolomide Capsules must be adjusted according to nadir neut ophil and platelet counts in he previous cycle and he neut ophil and platelet counts at he time of initiating he next cycle. For temozolomide dosage calculations based on body surface area (BSA) see Table 5. For suggested capsule combinations on a daily dose see Table 6.

Patients with Refractory Anaplastic Astrocytoma

For adults the initial dose is 150 mg/m^2 orally once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if bo h the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are ≥ 1.5 x 10^9/L (1,500/µL) and both he nadir and Day 29, Day 1 of next cycle platelet counts are ≥ 100 x 10^9/L (100,000/µL), he temozolomide dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after he first dose) or within 48 hours of that day, and weekly until he ANC is above 1.5 x 10^9/L (1,500/µL) and he platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of temozolomide should not be started until he ANC and platelet count exceed hese levels. If the ANC falls to <1.0 x 10^9/L (1,000/µL) or he platelet count is <50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, he lowest recommended dose (see Table 4). Temozolomide herapy can be continued until disease p ogression. In he clinical trial, treatment could be continued for a maximum of 2 years; but he optimum duration of therapy is not known.

Table 4 Dosing Modification Table

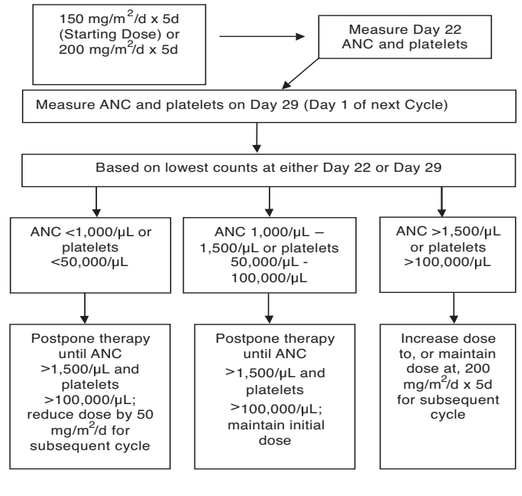

Table 5
Daily Dose Calculations by Body Surface Area (BSA)

Total BSA (m^2)	75 mg/m^2 (mg daily)	150 mg/m^2 (mg daily)	200 mg/m^2 (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480
2.5	187.5	375	500

Table 6
Suggested Capsule Combinations Based on Daily Dose in Adults
Number of Daily Capsules by Strength (mg)

Total Daily Dose (mg)	250 mg	180 mg	140 mg	100 mg	20 mg	5 mg
75	0	0	0	0	3	3
82.5	0	0	0	0	4	0
90	0	0	0	0	4	2
97.5	0	0	0	1	0	0
105	0	0	0	1	0	1
112.5	0	0	0	1	0	2
120	0	0	0	1	1	0
127.5	0	0	0	1	1	1
135	0	0	0	1	1	3
142.5	0	0	1	0	0	0
150	0	0	1	0	0	2
157.5	0	0	1	0	1	0
165	0	0	1	0	1	1
172.5	0	0	1	0	1	2
180	0	1	0	0	0	0
187.5	0	1	0	0	0	1
195	0	1	0	0	0	3
200	0	1	0	0	1	0
210	0	0	0	2	0	2
220	0	0	0	2	1	0
225	0	0	0	2	1	1
240	0	0	1	1	0	0
255	1	0	0	0	0	1
260	1	0	0	0	0	2
270	1	0	0	0	2	0
280	0	0	2	0	0	0
285	0	0	2	0	0	1
300	0	0	0	3	0	0
315	0	0	0	3	0	3
320	0	1	1	0	0	0
330	0	1	1	0	0	2
340	0	1	1	0	1	0
345	0	1	1	0	1	1
360	0	2	0	0	0	0
375	0	2	0	0	0	3
380	0	1	0	2	0	0
400	0	0	0	4	0	0
420	0	0	3	0	0	0
440	0	0	3	0	1	0
460	0	2	0	1	0	0
480	0	1	0	3	0	0
500	2	0	0	0	0	0

In clinical trials, temozolomide was administered under both fasting and non-fasting conditions; however, absorption is affected by food (see CLINICAL PHARMACOLOGY) and consistency of administration wi h respect to food is recommended. There are no dietary restrictions with temozolomide. To reduce nausea and vomiting, temozolomide should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic herapy may be administered prior to and/or following administration of temozolomide capsules.

Temozolomide Capsules should not be opened or chewed. They should be swallowed whole wi h a glass of water.

Handling and Disposal

Temozolomide causes he rapid appearance of malignant tumors in rats. Capsules should not be opened. If capsules are accidentally opened or damaged, rigo ous precautions should be taken with he capsule contents to avoid inhalation or contact wi h he skin or mucous membranes. P ocedures for p oper handling and disposal of anticancer drugs should be considered[1-7]. Several guidelines on this subject have been published. There is no general agreement hat all of the p ocedures recommended in he guidelines are necessary or app opriate.

HOW SUPPLIED

Temozolomide Capsules are available as:

5 mg: Off-white opaque cap and off-white opaque body filled with white to off-white powder. Imprinted in green ink stylized **barr** over **5 mg** on one piece and **1078** on he other piece.
Available in bottles of:
5 Capsules NDC 0555-1078-52
20 Capsules NDC 0555-1078-18

20 mg: Off-white opaque cap and off-white opaque body filled wi h white to off-white powder. Imprinted in b own ink stylized **barr** over **20 mg** on one piece and **1077** on he other piece.
Available in bottles of:
5 Capsules NDC 0555-1077-52
20 Capsules NDC 0555-1077-18

100 mg: Off-white opaque cap and off-white opaque body filled with off-white or light tan/light pink powder. Imprinted in blue ink stylized **barr** over **100 mg** on one piece and **1076** on he o her piece.
Available in bottles of:
5 Capsules NDC 0555-1076-52
20 Capsules NDC 0555-1076-18

140 mg: Blue opaque cap and off-white opaque body filled wi h off-white or light tan/light pink powder. Imprinted in black ink stylized **barr** over **140 mg** on one piece and **1159** on the other piece.
Available in bottles of:
5 Capsules NDC 0555-1159-52
20 Capsules NDC 0555-1159-18

180 mg: Dark orange opaque cap and off-white opaque body filled wi h off-white or light tan/light pink powder. Imprinted in black ink stylized **barr** over **180 mg** on one piece and **1160** on he o her piece.
Available in bottles of:
5 Capsules NDC 0555-1160-52
20 Capsules NDC 0555-1160-18

250 mg: Off-white opaque cap and off-white opaque body filled with off-white or light tan/light pink powder. Imprinted in black ink stylized **barr** over **250 mg** on one piece and **1075** on the other piece.
Available in bottles of:
5 Capsules NDC 0555-1075-52
20 Capsules NDC 0555-1075-18

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

REFERENCES

1. Recommendations for he Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Gove nment Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. *JAMA.* 1985;2.53(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available f om Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Heal h Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia.* 1983;1:426-428.
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6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.* 1990;47:1033-1049.
7. Cont olling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm.* 1996;53:1669-1685.

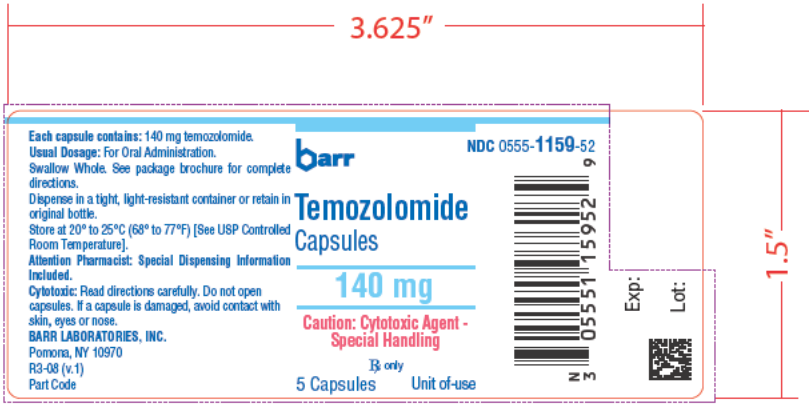
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised APRIL 2008
BR-1075, 1076, 1077, 1078, 1159, 1160

Barr Laboratories, Inc.

Item: Temozolomide 140 mg 5ct
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 15952 9
MATRIX: Part Code
BARCODE VERIFICATION:
UPC: ANSI X3.182 Grade "B"+
MATRIX: ECC 70
SIZE: 3.625" X 1.5" (R=0.0625)
PRINT TO CUT : ±1/32" (0.8mm)
WEB REWIND: #4
Ssplices: NMT 2
STOCK: TBD

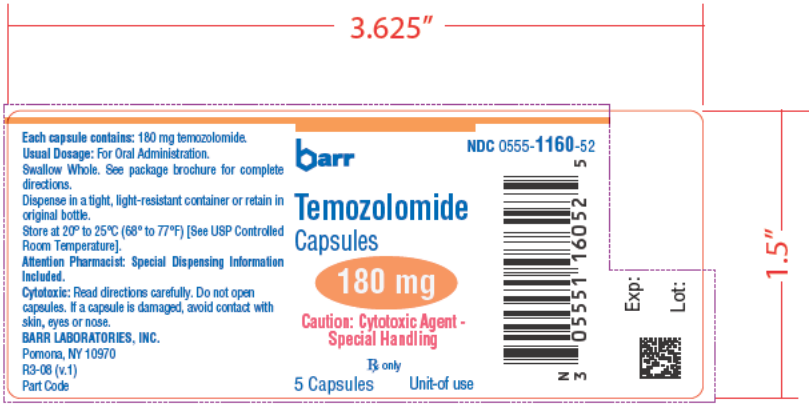
(b) (4)



Barr Laboratories, Inc.

Item: Temozolomide 180 mg 5ct
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 16052 5
MATRIX: Part Code
BARCODE VERIFICATION:
UPC: ANSI X3.182 Grade "B"+
MATRIX: ECC 70
SIZE: 3.625" X 1.5" (R=0.0625)
PRINT TO CUT : ±1/32" (0.8mm)
WEB REWIND: #4
SPLICES: NMT 2
STOCK: TBD

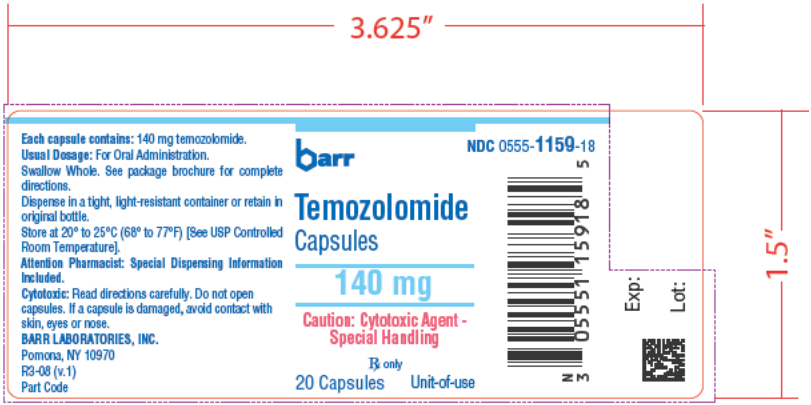
(b) (4)



Barr Laboratories, Inc.

Item: Temozolomide 140 mg 20ct
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 15918 5
MATRIX: Part Code
BARCODE VERIFICATION:
UPC: ANSI X3.182 Grade "B"+
MATRIX: ECC 70
SIZE: 3.625" X 1.5" (R=0.0625)
PRINT TO CUT : ±1/32" (0.8mm)
WEB REWIND: #4
SPLICES: NMT 2
STOCK: TBD

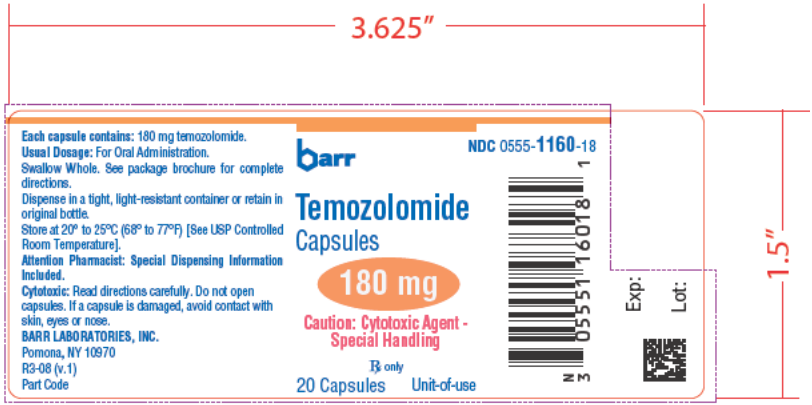
(b) (4)



Barr Laboratories, Inc.

Item: Temozolomide 180 mg 20ct
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 16018 1
MATRIX: Part Code
BARCODE VERIFICATION:
UPC: ANSI X3.182 Grade "B"+
MATRIX: ECC 70
SIZE: 3.625" X 1.5" (R=0.0625)
PRINT TO CUT : ±1/32" (0.8mm)
WEB REWIND: #4
Ssplices: NMT 2
STOCK: TBD

(b) (4)



Barr Laboratories, Inc.

ITEM: Temozolomide 140 mg 5 ct
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 15952 9
C128 READS: Part Code
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
140 mg

Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 140 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
Part Code
R3-08 (v.1)

C07146 16SBS

NDC 0555-1159-52

barr

Temozolomide
Capsules

140 mg

For Oral Administration

N 3 05551 15952 9

NDC 0555-1159-52

barr

Temozolomide
Capsules

140 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
5 Capsules
Unit-of-Use

NDC 0555-1159-52

barr

Temozolomide
Capsules

140 mg

For Oral Administration

℞ only
5 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 180 mg 5ct
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 16052 5
C128 READS: Part Code
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
180 mg

Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 180 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
Part Code
R3-08 (v.1)

C07146 16SBS

NDC 0555-1160-52

barr

Temozolomide
Capsules

180 mg

For Oral Administration

N 3 05551 16052 5

NDC 0555-1160-52

barr

Temozolomide
Capsules

180 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
5 Capsules
Unit-of-Use

NDC 0555-1160-52

barr

Temozolomide
Capsules

180 mg

For Oral Administration

℞ only
5 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 140 mg, 20 count
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 15918 5
C128 READS: Part Code
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
140 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 140 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
Part Code
R3-08 (v.1)

C07146 16SBS

NDC 0555-1159-18

barr

Temozolomide
Capsules
140 mg
For Oral Administration

N 3 05551 15918 5

NDC 0555-1159-18

barr

Temozolomide
Capsules
140 mg
For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
20 Capsules
Unit-of-Use

NDC 0555-1159-18

barr

Temozolomide
Capsules
140 mg
For Oral Administration

℞ only
20 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 180 mg, 20 count
PART: Part Code R3-08 (v.1)
UPC: N/3 05551 160181
C128 READS: Part Code
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
180 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 180 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
Part Code
R3-08 (v.1)

C07146 16SBS

NDC 0555-1160-18

barr

Temozolomide
Capsules

180 mg

For Oral Administration

N 3 05551 16018 1

NDC 0555-1160-18

barr

Temozolomide
Capsules

180 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
20 Capsules
Unit-of-Use

NDC 0555-1160-18

barr

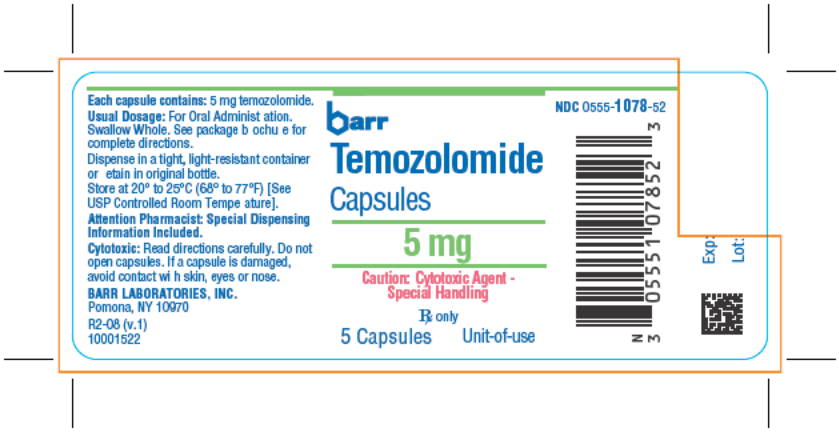
Temozolomide
Capsules

180 mg

For Oral Administration

℞ only
20 Capsules
Unit-of-Use

(b) (4)



Black	UV Skip Varnish	PMS	(b) (4)
PMS (b) (4)	Die Strike	PMS	

Customer: Barr

PO#:

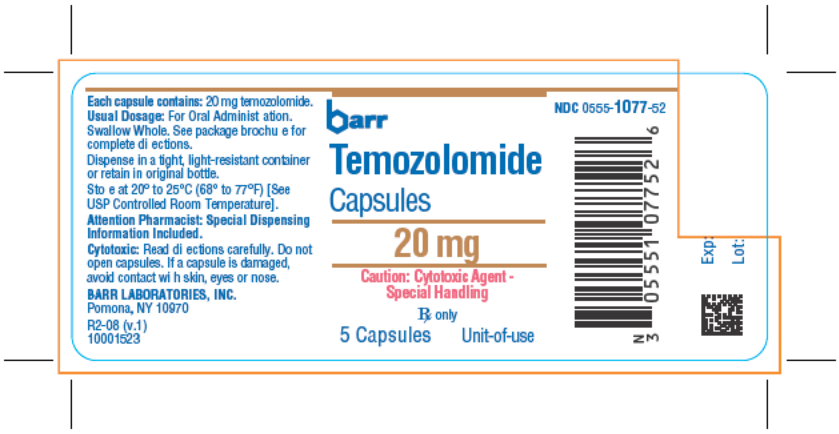
Job #: 165121-1

Size: 1.5" X 3.625"

Comments: UV Skip Varnish .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)



Black	UV Skip Varnish	PMS	(b) (4)
PMS (b) (4)	Die Strike	PMS	

Customer: Barr

PO#:

Job #: 165123-1

Size: 1.5" X 3.625"

Comments: UV Skip Varnish Area .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)

Black
UV Skip Varnish
PMS (b) (4)
PMS (b) (4)
Die Strike

Customer: Barr
PO#:
Job #: 165126-2
Size: 1.5" X 3.625"
Comments: UV Skip Varnish Area .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)

Black
PMS (b) (4)
Die Strike
PMS (b) (4)
UV Skip Varnish

Customer: Barr
PO#:
Job #: 165129-1
Size: 1.5" X 3.625"
Comments: UV Skip Varnish Area .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)

PMS (b) (4) Black

PMS (b) (4) PMS

UV Skip Varnish Die Strike

Customer: Barr

PO#:

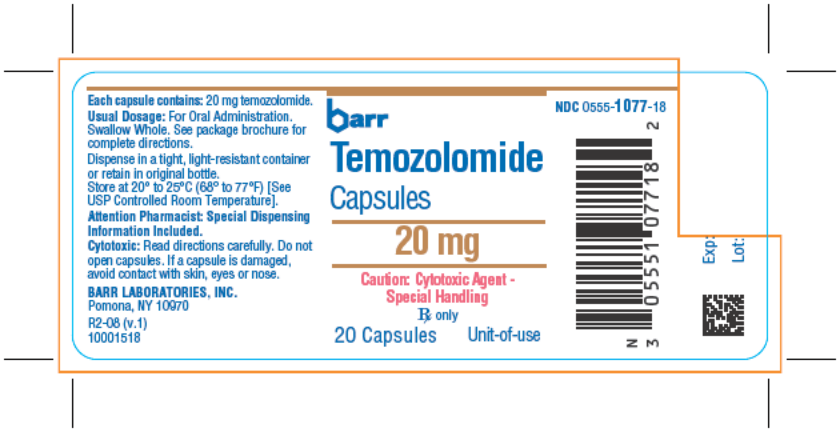
Job #: 165119-2

Size: 1.5" X 3.625"

Comments: UV Skip Varnish Area .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)



Black	UV Skip Varnish	PMS	(b) (4)
PMS (b) (4)	Die Strike	PMS	

Customer: Barr

PO#:

Job #: 165124-2

Size: 1.5" X 3.625"

Comments: UV Skip Varnish Area .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)

Black
UV Skip Varnish
PMS (b) (4)
Die Strike
PMS (b) (4)

Customer: Barr
PO#:
Job #: 165128-1
Size: 1.5" X 3.625"
Comments: UV Skip Varnish Area .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

(b) (4)

Black
UV Skip Varnish
Die Strike
PMS (b) (4)
PMS (b) (4)

Customer: Barr
PO#:
Job #: 165130-1
Size: 1.5" X 3.625"
Comments: UV Skip Varnish .4687" X .8437"

	PROOFED BY:	DATE
INITIAL SET BY:		
CORRECTED BY:		
CLIENTS APPROVAL BY:		
PRIVATE CUSTOMER APPROVAL BY:		

Barr Laboratories, Inc.

ITEM: Temozolomide 5 mg
PART: 15001207 R2-08 (v.1)
UPC: N/3 05551 07852 3
C128 READS: 15001207
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
5 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 5 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001207
R2-08 (v.1)

C07146 16SBS

NDC 0555-1078-52

barr

Temozolomide
Capsules

5 mg

For Oral Administration

N/3 05551 07852 3

NDC 0555-1078-52

barr

Temozolomide
Capsules

5 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
5 Capsules
Unit-of-Use

NDC 0555-1078-52

barr

Temozolomide
Capsules

5 mg

For Oral Administration

℞ only
5 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 20 mg
PART: 15001203 R2-08 (v.1)
UPC: N/3 05551 07752 6
C128 READS: 15001203
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
20 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 20 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001203
R2-08 (v.1)

C07146 16SBS

NDC 0555-1077-52

barr

Temozolomide
Capsules

20 mg

For Oral Administration

N/3 05551 07752 6

NDC 0555-1077-52

barr

Temozolomide
Capsules

20 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
5 Capsules
Unit-of-Use

NDC 0555-1077-52

barr

Temozolomide
Capsules

20 mg

For Oral Administration

℞ only
5 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 100 mg
PART: 15001201 R2-08 (v.1)
UPC: N/3 05551 07652 9
C128 READS: 15001201
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
100 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 100 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001201
R2-08 (v.1)

C07146 16SBS

NDC 0555-1076-52

barr

Temozolomide
Capsules

100 mg

For Oral Administration

N/3 05551 07652 9

NDC 0555-1076-52

barr

Temozolomide
Capsules

100 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
5 Capsules
Unit-of-Use

NDC 0555-1076-52

barr

Temozolomide
Capsules

100 mg

For Oral Administration

℞ only
5 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 250 mg
PART: 15001205 R2-08 (v.1)
UPC: N/3 05551 07552 2
C128 READS: 15001205
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
250 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 250 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001205
R2-08 (v.1)

C07146 16SBS

NDC 0555-1075-52

barr

Temozolomide
Capsules

250 mg

For Oral Administration

N/3 05551 07552 2

NDC 0555-1075-52

barr

Temozolomide
Capsules

250 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
5 Capsules
Unit-of-Use

NDC 0555-1075-52

barr

Temozolomide
Capsules

250 mg

For Oral Administration

℞ only
5 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 5 mg
PART: 15001206 R2-08 (v.1)
UPC: N/3 05551 07818 9
C128 READS: 15001206
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
5 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 5 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001206
R2-08 (v.1)

C07146 16SBS

NDC 0555-1078-18

barr

Temozolomide
Capsules

5 mg

For Oral Administration

N/3 05551 07818 9

NDC 0555-1078-18

barr

Temozolomide
Capsules

5 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
20 Capsules
Unit-of-Use

NDC 0555-1078-18

barr

Temozolomide
Capsules

5 mg

For Oral Administration

℞ only
20 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 20 mg
PART: 15001202 R2-08 (v.1)
UPC: N/3 05551 07718 2
C128 READS: 15001202
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
20 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 20 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001202
R2-08 (v.1)

C07146 16SBS

NDC 0555-1077-18

barr

Temozolomide
Capsules

20 mg

For Oral Administration

N/3 05551 07718 2

NDC 0555-1077-18

barr

Temozolomide
Capsules

20 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
20 Capsules
Unit-of-Use

NDC 0555-1077-18

barr

Temozolomide
Capsules

20 mg

For Oral Administration

℞ only
20 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 100 mg
PART: 15001200 R2-08 (v.1)
UPC: N/3 05551 07618 5
C128 READS: 15001200
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
100 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 100 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001200
R2-08 (v.1)

C07146 16SBS

NDC 0555-1076-18

barr

Temozolomide
Capsules

100 mg

For Oral Administration

N 3 05551 07618 5

NDC 0555-1076-18

barr

Temozolomide
Capsules

100 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
20 Capsules
Unit-of-Use

NDC 0555-1076-18

barr

Temozolomide
Capsules

100 mg

For Oral Administration

℞ only
20 Capsules
Unit-of-Use

Barr Laboratories, Inc.

ITEM: Temozolomide 250 mg
PART: 15001204 R2-08 (v.1)
UPC: N/3 05551 07518 8
C128 READS: 15001204
BBARCODE VERIFICATION: C128 & UPC: ANSI Grade "B" or Better Pass Traditional
SIZE: 2.25" x 2.25" x 4.5"
DESIGN: C07146
STOCK: .016 SBS

(b) (4)

Temozolomide
Capsules
250 mg
Attention Pharmacist: Special Dispensing Information Included.

Each capsule contains: 250 mg temozolomide.

Usual Dosage: For Oral Administration. Swallow Whole. See package brochure for complete directions.

Dispense in a tight, light-resistant container or retain in original bottle.

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

Attention Pharmacist: Special Dispensing Information Included.

Cytotoxic: Read directions carefully. Do not open capsules. If a capsule is damaged, avoid contact with skin, eyes or nose.

Caution: Cytotoxic Agent - Special Handling

barr

BARR LABORATORIES, INC.
Pomona, NY 10970
15001204
R2-08 (v.1)

C07146 16SBS

NDC 0555-1075-18

barr

Temozolomide
Capsules

250 mg

For Oral Administration

N/3 05551 07518 8

NDC 0555-1075-18

barr

Temozolomide
Capsules

250 mg

For Oral Administration

Caution: Cytotoxic Agent - Special Handling

℞ only
20 Capsules
Unit-of-Use

NDC 0555-1075-18

barr

Temozolomide
Capsules

250 mg

For Oral Administration

℞ only
20 Capsules
Unit-of-Use

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

LABELING REVIEWS

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

ANDA Number: 78-879 Date of Submission: June 1, 2007 and Mar 19, 2007

Applicant's Name: Barr laboratories

Established Name: Temozolomide Capsule 5 mg, 20 mg, 100 mg, and 250 mg

---

Labeling Deficiencies: June 1, 2007 submission revised May 2007.

1. CONTAINER - 5s and 20s unit- of -use bottles

   Decrease the prominence of the total content. We recommend decreasing the font size and do not highlight. It appears to be in close proximity to the product strength and the 20 package size could be mistaken as the strength. Please ensure the caps for the uit-of-use bottles are child resistant. Ensure each strength is differentiated by the color codes used for the innovator product that corresponds to the color band around the capsules.

2. PROFESSIONAL INSERT- You stated in your patent and exclusivity statement that you do not plan to include the ODE and I-450 indications in your labeling. Please ensure text regarding these indications are carved out of your labeling. We specifically refer you to the following sections: WARNINGS, second paragraph; PRECAUTIONS, Laboratories Tests, first sentence and; ADVERSE REACTIONS, first section and table 1 prior to Refractory Anaplastic Astrocytoma subsection.

3. PATIENT INSERT - Remove the following text regarding I-450 seen under How should I take Temozolomide, third paragraph "for 42 days (up to 49) with radiotherapy. Another". In addition, use the full established name in the running text.

4. PHARMACIST INFORMATION SHEET- Delete text regarding the protected exclusivities for ODE (Newly Diagnosed High grade Gliomas concomitantly with Radiotherapy and then as maintenance therapy and the associated I-450 exclusivities "Newly diagnosed Concomitant Phase treatment Schedule" followed by the Maintenance Phase treatment Schedule subsections found in the pharmacist information sheet.

Revise your labels 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 and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-879
Date of Submission	
Applicant	Barr
Drug Name	Temozolomide capsule
Strength(s)	5 mg, 20 mg, 100 mg, 250 mg

LABELS AND LABELING

Container Labels	**Submitted Draft**
5s and 20s	
Carton Labeling	
Package Insert Labeling	
Patient instruction sheet	

BASIS OF APPROVAL:

Patent Data For NDA 21-029

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5260291	AUG 11, 2013 Peds Feb, 11, 2014	U-619	TREATMENT OF MALIGNANT NEOPLASM	PIV	Same As

Exclusivity Data for NDA 21-029

Code/sup	Expiration	Description	Labeling impact
ODE	3/15/2012	Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment	Carved out
SE-008/I-450	3/15/2008	Treatment of patients with newly diagnosed high grade glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment	Carved Out

Reference Listed Drug

RLD on the 356(h) form	Temodar
NDA Number	21-029
RLD established name	Temozolomide
Firm	Schering;Plough Research Institute
Currently approved PI	S-011
AP Date	31 MAR 2006

Note: RLD has (b) (4) supplements

NOTES/QUESTIONS TO THE CHEMIST: The firm has several iron containing ingredients could you confirm that the total daily dose for iron does not exceed 5 mg/day. Thanks

---

FOR THE RECORD:

1. Review based on the labeling of the RLD NDA 21-029/S-011, approved Mar 31, 2006. SE8- Mar 15, 2005
2. Patent/ Exclusivities: See above.
3. Storage Conditions:
   NDA – CRT (20 -25C), ANDA - Same as RLD, USP - N/A
4. Dispensing Recommendations: None
   NDA – ANDA USP -
5. Scoring: None NDA -ANDA –
6. **Product Line:**
   RLD: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg (5s, 14s, 20s). White or off White capsules with color bands Green. Brown, Blue, Red, Black imprint and color coded are important

   ANDA: 5 mg, 20 mg, 100 mg and 250 mg (5s and 20s) Color bands are the same

   The applicant proposes to market their product The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). N/A product contains iron oxide. Iron consumption per day must not exceed 5 mg/day.

8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

Date of Review: Oct 05, 2007 **Date of Submission: 1 JUN and 19 MAR 2007**

Primary Reviewer: Angela Payne, RPh **Date:**

Team Leader: John Grace, RPh **Date:**

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cc: ANDA: 78-879
DUP/DIVISION FILE
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Review - draft

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
10/15/2007 09:54:54 AM
LABELING REVIEWER

John Grace
10/19/2007 10:10:34 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-879 Date of Submission: 20 DEC 2007

Applicant's Name: Barr laboratories

Established Name: Temozolomide Capsule 5 mg, 20 mg, 100 mg, and 250 mg

---

Labeling Deficiencies:

1. CONTAINER - 5s and 20s unit- of -use bottles

   a. Add to the dispensing statement - "or retain in original bottle." In addition, place "Caution: Cytotoxic agent- Special Handling" in red print on the pain panel rather than the side panel for prominence.

   b. We recommend providing a carton to protect the consumer from the possibility of glass breakage that may result in damage to the capsules and direct patient/consumer contact with the drug content.

2. PROFESSIONAL INSERT-

   a. You stated in your patent and exclusivity statement that you do not plan to include the ODE and I-450 indications in your labeling. Please ensure that the text regarding these indications is carved out of your labeling. We specifically refer you to the following section: PRECAUTIONS, Geriatrics. 3rd paragraph.

   b. Prior to the Description section place a statement informing the pharmacist that a patient information and pharmacist's information sheets are attached.

3. PATIENT INSERT -

   a. Please explain the accessibility of the patient information sheet to the patient. Will the patient information sheet become a separate sheet attached to the bottle, inside the bottle, on a pad, etc? How will the pharmacist obtain the information sheet to give to the patient?

   b. Add "Pharmacist: Tear at perforations and give to patients."

4. PHARMACIST INFORMATION SHEET- Satisfactory.

Revise your labels 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 and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

SUMMARY
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-879
Date of Submission	
Applicant	Barr
Drug Name	Temozolomide capsule
Strength(s)	5 mg, 20 mg, 100 mg, 250 mg

LABELS AND LABELING	
Container Labels	**Submitted Draft**
5s and 20s	\\Cdsesub1\nonectd\N78879\N_000\2007-12-20\Module 1\Module 1.14\1.14.1.1 Final Print Container Labels.pdf
Carton Labeling	
Package Insert	
Patient instruction	
Pharmacist sheet	

REFERENCE LISTED:

Patent Data For NDA 21-029

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5260291	AUG 11, 2013 Peds Feb, 11, 2014	U-619	TREATMENT OF MALIGNANT NEOPLASM	PIV	Same As

Exclusivity Data for NDA 21-029

Code/sup	Expiration	Description	Labeling impact
ODE	3/15/2012	Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment	Carved out
SE-008/I-450	3/15/2008	Treatment of patients with newly diagnosed high grade glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment	Carved Out. Falls under the ODE listed in the box above.

Reference Listed Drug

RLD on the 356(h) form	Temodar
NDA Number	21-029
RLD established name	Temozolomide Capsules
Firm	Schering-Plough Research Institute
Currently approved PI	S-011
AP Date	31 MAR 2006

Note: RLD has (b) (4)

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of the RLD NDA 21-029/S-011, approved Mar 31, 2006. SE8- Mar 15, 2005
2. Patent/ Exclusivities: See above.
3. Storage Conditions:
   NDA – CRT (20 -25C), ANDA - Same as RLD, USP - N/A
4. Dispensing Recommendations: None
   NDA – ANDA USP -
5. Scoring: None NDA -ANDA –
6. **Product Line:**
   RLD: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg (5s, 14s, 20s). White or off White capsules with color bands Green. Brown, Blue, Red, Black imprint and color coded are important

   ANDA: 5 mg, 20 mg, 100 mg and 250 mg (5s and 20s) Color bands are the same. 60cc, Glass, Amber, Wide Mouth, Round, (b) (4). Per chem. Review: The drug product will be packaged and stored in 5-unit and 20-unit (60 cc Amber Glass Bottle, 33 mm CRC Cap and (b) (4) (b) (4) Cotton Filler) container closure system.

7. The applicant proposes to market their product The tablet/capsule imprint(ings)/embossing(s) debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Chemistry review no 1 page 18 reveals iron consumption per day must not exceed 5 mg/day.

8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

Date of Review: 15 JAN 2008 **Date of Submission: 20 DEC 2007**

Primary Reviewer: Angela Payne, RPh **Date:**

Team Leader: John Grace, RPh **Date:**

cc: ANDA: 78-879
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
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Review - draft

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/s/

Angela Payne
1/17/2008 04:41:38 PM
LABELING REVIEWER

John Grace
1/28/2008 12:41:28 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-879 Date of Submission: 18 FEB 2008, 21 MAR 2008, and 25 MAR 2008

Applicant's Name: Barr laboratories

Established Name: Temozolomide Capsule 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

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Labeling Deficiencies:

1. CONTAINER - 5s and 20s unit- of -use bottles- Satisfactory.

2. CARTONS (1s)- Satisfactory.

3. PROFESSIONAL INSERT-

PRECAUTIONS, Pediatric subsection- Delete (b) (4) from the footnote section found following the table.

4. PATIENT INSERT - Satisfactory in draft.

5. PHARMACIST INFORMATION SHEET- Satisfactory in draft.

Revise your labels 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 and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD

1. APPLICANT INFORMATION:

ANDA Number	78-879
Date of Submission	
Applicant	Barr
Drug Name	Temozolomide Capsule
Strength(s)	5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

LABELS AND LABELING	
Container Labels 5s and 20s	Submitted Draft
Carton Labeling	
Package Insert Patient instruction	
Pharmacist sheet	

2. NOTES/QUESTIONS TO THE CHEMIST:

3. Review based on the labeling of the RLD NDA 21-029/S-011, Approved Mar 31, 2006. SE8- Mar 15, 2005.

Reference Listed Drug	
RLD on the 356(h) form	Temodar
NDA Number	21-029
RLD established name	Temozolomide Capsules
Firm	Schering-Plough Research Institute
Currently approved PI	S-011
AP Date	31 MAR 2006
Note: RLD has (b) (4) supplements	

4. Patent/ Exclusivities: See above. REFERENCE LISTED:

Patent Data For NDA 21-029

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5260291	AUG 11, 2013 Peds Feb, 11, 2014	U-619	TREATMENT OF MALIGNANT NEOPLASM	PIV	Same As

Exclusivity Data for NDA 21-029

Code/sup	Expiration	Description	Labeling impact
ODE	3/15/2012	Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment	Carved out

SE-008/I-450	3/15/2008	Treatment of patients with newly diagnosed high grade glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment	Carved Out. Falls under the ODE listed in the box above.

5. Storage Conditions:
   NDA – CRT (20 -25C), ANDA - Same as RLD, USP - N/A
6. Dispensing Recommendations: None
   NDA – ANDA USP -
7. Scoring: None NDA -ANDA –
8. Product Line:
   RLD: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg (5s, 14s, 20s). White or off White capsules with color bands Green. Brown, Blue, Red, Black imprint and color coded are important

   ANDA: 5 mg, 20 mg, 100 mg and 250 mg (5s and 20s) Color bands are the same. 60cc, Glass, Amber, Wide Mouth, Round, (b) (4). Per chem. Review: The drug product will be packaged and stored in 5-unit and 20-unit (60 cc Amber Glass Bottle, 33 mm CRC Cap and (b) (4) (b) (4) Cotton Filler) container closure system.

9. The applicant proposes to market their product The tablet/capsule imprint(ings)/embossing(s) debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Chemistry review no 1 page 18 reveals iron consumption per day must not exceed 5 mg/day.

10. Inactive Ingredients:
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

Date of Review: 4/04/08 Date of Submission: 18 FEB 2008, 21 MAR 2008, and 25 MAR 2008

Primary Reviewer: Angela Payne, RPh Date:

Team Leader: John Grace, RPh Date:

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cc: ANDA: 78-879
DUP/DIVISION FILE
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Review - draft

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/s/

Angela Payne
4/4/2008 12:20:54 PM
LABELING REVIEWER

John Grace
4/8/2008 09:42:21 AM
LABELING REVIEWER

APPROVAL SUMMARY #1
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	78-879
Date of Submission	16 APR 2008
Applicant	Barr
Drug Name	Temozolomide Capsule
Strength(s)	5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

LABELS AND LABELING - Satisfactory in FPL	
Container Labels 5s and 20s	Satisfactory March 21, 2008 \\Fdswa150\nonectd\N78879\N_000\2008-03-21\Module 1\Module 1.14\1.14.1.1 Draft Container and Carton Labels.pdf
Carton Labeling	Satisfactory March 21, 2008 \\Fdswa150\nonectd\N78879\N_000\2008-03-21\Module 1\Module 1.14\1.14.1.1 Draft Container and Carton Labels.pdf
Professional insert, Pharmacist leaflet, and Patient Leaflet- Satisfactory April 16, 2008- FPL \\Fdswa150\nonectd\N78879\N_000\2008-04-16\Module 1\Module 1.14\1.14.1.3 Final Package Insert.pdf	

2. NOTES/QUESTIONS TO THE CHEMIST:

3. Review based on the labeling of the RLD NDA 21-029/S-011, Approved Mar 31, 2006. SE8- Mar 15, 2005.

Reference Listed Drug	
RLD on the 356(h) form	Temodar
NDA Number	21-029
RLD established name	Temozolomide Capsules
Firm	Schering-Plough Research Institute
Currently approved PI	S-011
AP Date	31 MAR 2006
Note: RLD has [redacted] (b) (4) supplements	

4. Patent/ Exclusivities: See above. REFERENCE LISTED:

Patent Data For NDA 21-029

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5260291	AUG 11, 2013 Peds Feb, 11, 2014	U-619	TREATMENT OF MALIGNANT NEOPLASM	PIV	Same As

Exclusivity Data for NDA 21-029

Code/sup	Expiration	Description	Labeling impact

ODE	3/15/2012	Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment	Carved out
SE-008/I-450	3/15/2008	Treatment of patients with newly diagnosed high grade glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment	Carved Out. Falls under the ODE listed in the box above.

5. Storage Conditions:
   NDA – CRT (20 -25C), ANDA - Same as RLD, USP - N/A
6. Dispensing Recommendations: None
   NDA – ANDA USP -
7. Scoring: None NDA -ANDA –
8. Product Line:
   RLD: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg (5s, 14s, 20s). White or off White capsules with color bands Green. Brown, Blue, Red, Black imprint and color coded are important

   ANDA: 5 mg, 20 mg, 100 mg and 250 mg (5s and 20s) Color bands are the same. 60cc, Glass, Amber, Wide Mouth, Round, (b) (4). Per chem. Review: The drug product will be packaged and stored in 5-unit and 20-unit (60 cc Amber Glass Bottle, 33 mm CRC Cap and (b) (4) (b) (4) Cotton Filler) container closure system.

9. The applicant proposes to market their product The tablet/capsule imprint(ings)/embossing(s) debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Chemistry review no 1 page 18 reveals iron consumption per day must not exceed 5 mg/day.

10. Inactive Ingredients:
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

Date of Review: 5/05/08 Date of Submission: APR 16, 2008

Primary Reviewer: Angela Payne, RPh Date:

Team Leader: John Grace, RPh Date:

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cc: ANDA: 78-879
DUP/DIVISION FILE
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Review

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/s/

Angela Payne
5/5/2008 08:20:11 AM
LABELING REVIEWER

John Grace
5/8/2008 10:16:32 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

CHEMISTRY REVIEWS

ANDA 78-879

Temozolomide Capsules, 5, 20, 100, and 250 mg

Barr Laboratories, Inc.

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA** # 78-879 (First Generic)

2. **REVIEW #:** 1

3. **REVIEW DATE:** 10-AUG-2007

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:**
   None

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Original ANDA	19-MAR-2007
Accepted for filing	14-JUN-2007

7. **NAME & ADDRESS OF APPLICANT:**

.

Name: Barr Laboratories, Inc.

Address: 223 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Representative Nicholas Tantillo
Telephone: (201) 930-3650
Facsimile: (631) 756-5114

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name N/A
   b) Non-Proprietary Name (USAN) Temozolomide Capsules

9. **LEGAL BASIS FOR SUBMISSION:**

The Reference Listed Drug (RLD) that is the basis for this submission is Temozolomide Capsules – Manufactured by Schereing, Inc, NDA .

10. **PHARMACOL. CATEGORY:** glioblastoma multiforme & refractory anaplastic astrocytoma

11. **DOSAGE FORM:** Capsules

12. **STRENGTH/POTENCY:** 5, 20, 100, and 250 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** __x_Rx ___OTC

15 **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) No**

(If applicable, fill out the form for special products and deliver to the team leader).

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

Chemical Name: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide

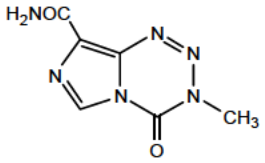
or

8-carbamoyl-3-methylimidazo[5.1-d]1,2,3,5-tetrazin-4(3H)-one

CAS #: 85622-93-1

USAN: Temozolomide

Molecular Structure:



Molecular Formula: $C_6H_6N_6O_2$

Molecular Weight: 194.15

17. **RELATED/SUPPORTING DOCUMENTS:**
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	10/05/07	(b) (4)
	III			4			
	III			4			

(b) (4)				(b) (4)
	4			
	4			
	4			

[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:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		
Other	N/A		

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 78-879

The Executive Summary

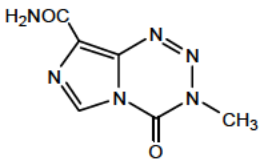
A. I. Recommendations

A. Recommendation and Conclusion on Approvability
The ANDA is not approvable for the following reasons:
There are deficiencies in the CMC portions of the ANDA.
Labeling and Bioequivalence reviews are pending.

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

B. II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
Capsules for oral administration contain temozolomide, an imidazotetrazine The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for Temozolomide Capsules are anhydrous lactose, colloidal silicon dioxide, povidone, sodium starch glycolate, stearic acid, and tartaric acid. The 5 mg, 20 mg, 100 mg, and 250 mg capsule shells contain D&C yellow no. 10, FD&C red no. 40, FD&C yellow no. 6, gelatin, and titanium dioxide. The 5 mg imprinting ink contains ammonium hydroxide, black iron oxide, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, and propylene glycol.

The 20 mg imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol, red iron oxide, shellac glaze, and yellow iron oxide. The 100 mg imprinting ink contains FD& C blue no. 1 aluminum lake, pharmaceutical grade shellac, polyvinylpyrrolidone, propylene glycol, sodium hydroxide, and titanium dioxide. The 250 mg imprinting ink contains D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake,

CLINICAL PHARMACOLOGY

Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

INDICATIONS AND USAGE

(b) (4)

Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

HOW SUPPLIED

Temozolomide Capsules are available as:

5 mg: Off-white opaque cap and off-white opaque body filled with white to off-white powder. Imprinted in green ink stylized barr over 5 mg on one piece and 1078 on the other piece. Available in bottles of:

5 Capsules NDC 0555-1078-52
20 Capsules NDC 0555-1078-18

20 mg: Off-white opaque cap and off-white opaque body filled with white to off-white powder. Imprinted in brown ink stylized barr over 20 mg on one piece and 1077 on the other piece. Available in bottles of:

5 Capsules NDC 0555-1077-52
20 Capsules NDC 0555-1077-18

100 mg: Off-white opaque cap and off-white opaque body filled with off-white or light tan/light pink powder. Imprinted in blue ink stylized barr over 100 mg on one piece and 1076 on the other piece. Available in bottles of:

5 Capsules NDC 0555-1076-52
20 Capsules NDC 0555-1076-18

250 mg: Off-white opaque cap and off-white opaque body filled with off-white or light tan/light pink powder. Imprinted in black ink stylized barr over 250 mg on one piece and 1075 on the other piece. Available in bottles of:

5 Capsules NDC 0555-1075-52
20 Capsules NDC 0555-1075-18

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

	Drug Substance	Drug Product Temozolomide Capsules
Maximum Daily Dose	500 mg	500 mg
Identification Threshold	0.10%	0.2%
Qualification Threshold	0.15%	0.2%

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable for the following reasons:
There are deficiencies in the CMC portions of the ANDA.
Labeling and Bioequivalence reviews are pending.

Following this page, 32 pages withheld in full (b)(4)

Chemistry Comments to be Provided to the Applicant

ANDA: 78-879 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules 5, 20, 100, and 250 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. DMF (b) (4) is inadequate. Please ensure a response from the DMF holder.

2. (b) (4)

3. Please include (b) (4)

4. Please modify (b) (4) .

5. Please develop (b) (4) .

6. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.

2. Information related to labeling and bioequivalency is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 78-879
Division File
Field Copy

Endorsements:

HFD-625/J. Wetzel/8/30/07
HFD-625/J. Fan/8/30/07
HFD-617/R. Adigun, PM, /8/30/07

F/T by:
\\cdsnas\ogds11\FIRMSAM\BARR\LTRS&REV\78879 REV1 jrw.doc

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/

Joseph Wetzel
11/2/2007 06:42:23 PM
CHEMIST

Rosalyn Adigun
11/7/2007 09:19:42 AM
CSO

James Fan
11/7/2007 01:03:32 PM
CHEMIST

ANDA 78-879

Temozolomide Capsules, 5, 20, 100, 140, 180, and 250 mg

Barr Laboratories, Inc.

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA** # 78-879 (First Generic)

2. **REVIEW #:** 2

3. **REVIEW DATE:** 18-SEP-2008

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:**

Original ANDA	19-MAR-2007
Accepted for filing	14-JUN-2007

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Amendment (Minor)	17-MAR-2008
Amendment (Major) (new strength 140 & 180 mg)	21-MAR-2008
New Correspondance	25-MAR-2008
Amendment (Gratuitous)	19-JUN-2008
Amendment (Telephone)	06-AUG-2008

7. **NAME & ADDRESS OF APPLICANT:**

.

Name:	Barr Laboratories, Inc.
Address:	223 Quaker Road P.O. Box 2900 Pomona, NY 10970
Representative:	Nicholas Tantillo
Telephone:	(201) 930-3650
Facsimile:	(631) 756-5114

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name	N/A
b) Non-Proprietary Name (USAN)	Temozolomide Capsules

9. **LEGAL BASIS FOR SUBMISSION:**

The Reference Listed Drug (RLD) that is the basis for this submission is Temozolomide Capsules – Manufactured by Schering, Inc, NDA 21029 .

10. **PHARMACOL. CATEGORY:** glioblastoma multiforme & refractory anaplastic astrocytoma

11. **DOSAGE FORM:** Capsules

12. **STRENGTH/POTENCY:** 5, 20, 100, 140, 180, and 250 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** __x_Rx ___OTC

15 **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) No**
(If applicable, fill out the form for special products and deliver to the team leader).

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

Chemical Name: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide

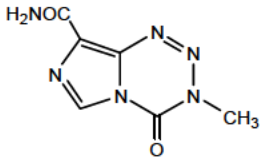
or

8-carbamoyl-3-methylimidazo[5.1-d]1,2,3,5-tetrazin-4(3H)-one

CAS #: 85622-93-1

USAN: Temozolomide

Molecular Structure:



Molecular Formula: $C_6H_6N_6O_2$

Molecular Weight: 194.15

17. **RELATED/SUPPORTING DOCUMENTS:**
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	adequate	7/18/08	(b) (4)
	III			4			
	III			4			

(b) (4)			(b) (4)			(b) (4)
	III		4			
	III		4			
	III		4			

[1] Action codes for DMF Table:

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2 –Type 1 DMF
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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:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/15/07	S. Ferguson
Methods Validation	N/A		
Labeling	approvable	5/8/08	A. Payne
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		
Other	N/A		

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 78-879

The Executive Summary

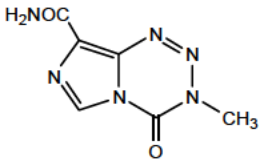
A. I. Recommendations

A. Recommendation and Conclusion on Approvability
The ANDA is not approvable for the following reasons:
There are deficiencies in the CMC portions of the ANDA.

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

B. II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
Capsules for oral administration contain temozolomide, an imidazotetrazine The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]- tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide. The inactive ingredients for Temozolomide Capsules are anhydrous lactose, colloidal silicon dioxide, povidone, sodium starch glycolate, stearic acid, and tartaric acid. The 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsule shells contain D&C yellow no. 10, FD&C red no. 40, FD&C yellow no. 6, gelatin, and titanium dioxide. The 140 mg capsule shell also contains D&C red no. 28, FD&C blue no. 1, and FD&C green no. 3. The 180 mg capsule shell also contains FD&C blue no. 1, FD&C red no. 40, and FD&C yellow no. 6. The 5 mg imprinting ink contains ammonium hydroxide, black iron oxide, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, and propylene glycol. The 20 mg imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol, red iron oxide, shellac glaze, and yellow iron oxide. The 100 mg imprinting ink contains FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, polyvinylpyrrolidone, propylene glycol, sodium hydroxide, and titanium dioxide. The 140 mg, 180

mg, and 250 mg 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, pharmaceutical glaze, propylene glycol, and synthetic black iron oxide.

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

(b) (4)

Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

	Drug Substance	Drug Product Temozolomide Capsules
Maximum Daily Dose	500 mg	500 mg
Identification Threshold	0.10%	0.20%
Qualification Threshold	0.15%	0.20%

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not approvable for the following reasons:
There are deficiencies in the CMC portions of the ANDA.

Following this page, 37 pages withheld in full (b)(4)

Chemistry Comments to be provided to the Applicant

ANDA: 78-879 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. Please revise and submit your drug product release specifications to include a *"Residual Solvents Test"* with test specifications listed as "Complies with USP <467>".

2. (b) (4)

3.

4.

5. Please provide your revised drug product COAs and your stability data sheets with actual data to reflect the above revisions.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available drug product room temperature stability data.

2. Labeling deficiencies were communicated to you via facsimile on May 8, 2008. You should address the issues in the May 8, 2008 communication prior to or concurrent with your response to this communication.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 78-879
Division File
Field Copy

Endorsements:

HFD-625/J. Wetzel/9/18/08
HFD-625/J. Fan/9/18/08
HFD-617/R. Adigun, PM, /9/18/08

F/T by:
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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/

Joseph Wetzel
11/12/2008 11:33:13 AM
CHEMIST

James Fan
11/12/2008 03:09:31 PM
CHEMIST

Rosalyn Adigun
11/13/2008 12:13:21 PM
CSO

ANDA 78-879

Temozolomide Capsules, 5, 20, 100, 140, 180, and 250 mg

Barr Laboratories, Inc.

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA** # 78-879 (First Generic)

2. **REVIEW #:** 3

3. **REVIEW DATE:** 25-JUN-2009

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:**

Original ANDA	19-MAR-2007
Accepted for filing	14-JUN-2007
Amendment (Minor)	17-MAR-2008
Amendment (Major) (new strength 140 & 180 mg)	21-MAR-2008
New Correspondance	25-MAR-2008
Amendment (Gratuitous)	19-JUN-2008
Amendment (Telephone)	06-AUG-2008

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Amendment (Minor)	06-FEB-2009
Amendment (Gratuitous)	19-JUN-2009

7. **NAME & ADDRESS OF APPLICANT:**

.

Name:	Barr Laboratories, Inc.
Address:	223 Quaker Road P.O. Box 2900 Pomona, NY 10970
Representative:	Nicholas Tantillo
Telephone:	(201) 930-3650
Facsimile:	(631) 756-5114

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name	N/A
b) Non-Proprietary Name (USAN)	Temozolomide Capsules

9. **LEGAL BASIS FOR SUBMISSION:**

The Reference Listed Drug (RLD) that is the basis for this submission is Temozolomide Capsules – Manufactured by Schering, Inc, NDA 21029 .

10. **PHARMACOL. CATEGORY:** glioblastoma multiforme & refractory anaplastic astrocytoma

11. **DOSAGE FORM:** Capsules

12. **STRENGTH/POTENCY:** 5, 20, 100, 140, 180, and 250 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** __x_Rx ___OTC

15 **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)** **No**
(If applicable, fill out the form for special products and deliver to the team leader).

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

Chemical Name: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide

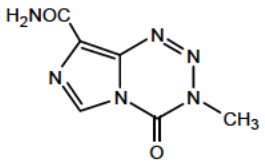
or

8-carbamoyl-3-methylimidazo[5.1-d]1,2,3,5-tetrazin-4(3H)-one

CAS #: 85622-93-1

USAN: Temozolomide

Molecular Structure:



Molecular Formula: $C_6H_6N_6O_2$

Molecular Weight: 194.15

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	adequate	6/24/09	(b) (4)
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)			(b) (4)			(b) (4)
	III		4			

[1] Action codes for DMF Table:

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[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:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/15/07	S. Fuerguson
Methods Validation	N/A		
Labeling	approvable	5/5/08	A. Payne
Bioequivalence	Acceptable	7/6/09	DL Mitchell
EA	N/A		
Radiopharmaceutical	N/A		
Other	N/A		

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 78-879

The Executive Summary

A. I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry is acceptable.
Labeling is acceptable.
Bio is acceptable.

ANDA is Approvable.

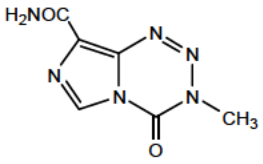
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

B. II. Summary of Chemistry Assessments

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

Capsules for oral administration contain temozolomide, an imidazotetrazine The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]- tetrazine-8-carboxamide. The structural formula is:



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

(b) (4)

Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

	Drug Substance	Drug Product Temozolomide Capsules
Maximum Daily Dose	500 mg	500 mg
Identification Threshold	0.10%	0.20%
Qualification Threshold	0.15%	0.20%

C. Basis for Approvability or Not-Approval Recommendation

Chemistry is acceptable.
Labeling is acceptable.
Bio is acceptable.

ANDA is Approvable.

Following this page, 40 pages withheld in full (b)(4)

Reviewer's Assessment:
The data were provided. Satisfactory

Comment 2:
Labeling deficiencies were communicated to you via facsimile on May 8, 2008. You should address the issues in the May 8, 2008 communication prior to or concurrent with your response to this communication.

Firm's Response 2: Adequate
The labeling deficiencies stated in the Agency's Labeling Comments dated April 08, 2008 have been addressed by Barr via a Labeling Amendment on April 16, 2008.

Note:
Labeling Review is acceptable, 5/5/08 (A. Payne).

cc: ANDA # 78-879
Division File
Field Copy

Endorsements:

HFD-625/J. Wetzel/6/24/09
HFD-625/J. Fan/6/24/09
HFD-617/S. Eng, PM, /6/24/09

F/T by:
\\Cdsnas1\OGDS11\Chemistry Division I\Team 3\FIRMSAM\BARR\LTRS&RVS\78879 REV3f jrw.doc
Approvable

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/s/

Joseph Wetzel
7/23/2009 10:54:44 AM
CHEMIST

James Fan
7/23/2009 01:12:35 PM
CHEMIST

Rosalyn Adigun
7/23/2009 01:19:18 PM
CSO

ANDA 78-879

Temozolomide Capsules, 5, 20, 100, 140, 180, and 250 mg

Barr Laboratories, Inc.

Joseph R. Wetzel
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. **ANDA** # 78-879 (First Generic)

2. **REVIEW #:** 3 Addendum

3. **REVIEW DATE:** 20-AUG-2009

4. **REVIEWER:** Joseph R. Wetzel

5. **PREVIOUS DOCUMENTS:**

Original ANDA	19-MAR-2007
Accepted for filing	14-JUN-2007
Amendment (Minor)	17-MAR-2008
Amendment (Major) (new strength 140 & 180 mg)	21-MAR-2008
New Correspondence	25-MAR-2008
Amendment (Gratuitous)	19-JUN-2008
Amendment (Telephone)	06-AUG-2008

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	**Document Date**
Amendment (Minor)	06-FEB-2009
Amendment (Gratuitous)	19-JUN-2009
Amendment (Telephone)	20-AUG-2009

7. **NAME & ADDRESS OF APPLICANT:**

.

Name:	Barr Laboratories, Inc.
Address:	223 Quaker Road P.O. Box 2900 Pomona, NY 10970
Representative:	Nicholas Tantillo
Telephone:	(201) 930-3650
Facsimile:	(631) 756-5114

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name	N/A
b) Non-Proprietary Name (USAN)	Temozolomide Capsules

9. **LEGAL BASIS FOR SUBMISSION:**

The Reference Listed Drug (RLD) that is the basis for this submission is Temozolomide Capsules – Manufactured by Schering, Inc, NDA 21029 .

10. **PHARMACOL. CATEGORY:** glioblastoma multiforme & refractory anaplastic astrocytoma

11. **DOSAGE FORM:** Capsules

12. **STRENGTH/POTENCY:** 5, 20, 100, 140, 180, and 250 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** __x_Rx ___OTC

15 **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)** **No**
(If applicable, fill out the form for special products and deliver to the team leader).

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

Chemical Name: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide

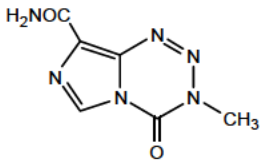
or

8-carbamoyl-3-methylimidazo[5.1-d]1,2,3,5-tetrazin-4(3H)-one

CAS #: 85622-93-1

USAN: Temozolomide

Molecular Structure:



Molecular Formula: $C_6H_6N_6O_2$

Molecular Weight: 194.15

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	adequate	6/24/09	(b) (4)
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)		(b) (4)			(b) (4)
	III	4			

[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:

None

18. **STATUS:**

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/15/07	S. Ferguson
Methods Validation	N/A		
Labeling	approvable	5/5/08	A. Payne
Bioequivalence	Acceptable	7/6/09	DL Mitchell
EA	N/A		
Radiopharmaceutical	N/A		
Other	N/A		

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 78-879

The Executive Summary

A. I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry is acceptable.
Labeling is acceptable.
Bio is acceptable.

ANDA is Approvable.

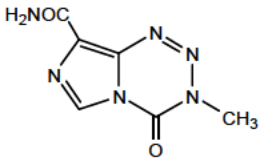
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

B. II. Summary of Chemistry Assessments

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

Capsules for oral administration contain temozolomide, an imidazotetrazine The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]- tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide. The inactive ingredients for Temozolomide Capsules are anhydrous lactose, colloidal silicon dioxide, povidone, sodium starch glycolate, stearic acid, and tartaric acid. The 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsule shells contain D&C yellow no. 10, FD&C red no. 40, FD&C yellow no. 6, gelatin, and titanium dioxide. The 140 mg capsule shell also contains D&C red no. 28, FD&C blue no. 1, and FD&C green no. 3. The 180 mg capsule shell also contains FD&C blue no. 1, FD&C red no. 40, and FD&C yellow no. 6. The 5 mg imprinting ink contains ammonium hydroxide, black iron oxide, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, and propylene glycol. The 20 mg imprinting ink contains ammonium hydroxide, black iron oxide, propylene glycol, red iron oxide, shellac glaze, and yellow iron oxide. The 100 mg imprinting ink contains FD&C blue no. 1 aluminum lake, pharmaceutical grade shellac, polyvinylpyrrolidone, propylene glycol, sodium hydroxide, and titanium dioxide. The 140 mg, 180 mg, and 250 mg 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, pharmaceutical glaze, propylene glycol, and synthetic black iron oxide.

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

(b) (4)

Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

	Drug Substance	Drug Product Temozolomide Capsules
Maximum Daily Dose	500 mg	500 mg
Identification Threshold	0.10%	0.20%
Qualification Threshold	0.15%	0.20%

C. Basis for Approvability or Not-Approval Recommendation

Chemistry is acceptable.
Labeling is acceptable.
Bio is acceptable.

ANDA is Approvable.

Following this page, 44 pages withheld in full (b)(4)

Reviewer's Assessment:
The data were provided. Satisfactory

Comment 2:
Labeling deficiencies were communicated to you via facsimile on May 8, 2008. You should address the issues in the May 8, 2008 communication prior to or concurrent with your response to this communication.

Firm's Response 2: Adequate
The labeling deficiencies stated in the Agency's Labeling Comments dated April 08, 2008 have been addressed by Barr via a Labeling Amendment on April 16, 2008.

Note:
Labeling Review is acceptable, 5/5/08 (A. Payne).

cc: ANDA # 78-879
Division File
Field Copy

Endorsements:

HFD-625/J. Wetzel/8/20/09
HFD-625/J. Fan/7/23/09
HFD-617/N. Patel, PM, /7/23/09

F/T by:
\\Cdsnas1\OGDS11\Chemistry Division I\Team 3\FIRMSAM\BARR\LTRS&RVS\78879 REV3f ADD jrw.doc
Approvable

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 78879	ORIG 1	BARR LABORATORIES INC	TEMOZOLOMIDE
ANDA 78879	ORIG 1	BARR LABORATORIES INC	TEMOZOLOMIDE
ANDA 78879	ORIG 1	BARR LABORATORIES INC	TEMOZOLOMIDE
ANDA 78879	ORIG 1	BARR LABORATORIES INC	TEMOZOLOMIDE
ANDA 78879	ORIG 1	BARR LABORATORIES INC	TEMOZOLOMIDE

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/s/

JOSEPH R WETZEL
08/21/2009
Approvable

JAMES M FAN
08/22/2009

NITIN K PATEL
08/24/2009

Final Approval Following a Tentative Approval
Abbreviated New Drug Application Regulatory Assessment

---

1. ANDA #
   078879

2. NAME AND ADDRESS OF APPLICANT
   Barr Laboratories, Inc.

3. LEGAL BASIS FOR SUBMISSION
   Final approval request due to the prosecution laches and/or inequitable conduct of the ‘291 patent

4. PROPRIETARY NAME
   Temodar Capsules

5. NONPROPRIETARY NAME
   Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

6. CURRENT SUBMISSIONS AND OTHER DATES:
   Patent amendment: December 22, 2009
   Minor amendment: January 29, 2010
   Telephone amendment: February 19, 2010

7. PHARMACOLOGICAL CATEGORY
   Glioblastoma multiforme & refractory anaplastic astrocytoma

8. Rx or OTC
   Rx

9. SAMPLES AND RESULTS
   N/A

10. LABELING STATUS
    Acceptable on May 28, 2008

11. BIOEQUIVALENCY STATUS
    Acceptable on July 6, 2009

12. MICROBIOLOGY STATUS
    N/A

13. ESTABLISHMENT INSPECTION
    Acceptable on November 15, 2007

14. CONCLUSIONS AND RECOMMENDATIONS
    ANDA was tentatively approved on September 10, 2009
    ANDA is recommended for full approval

PROJECT MANAGER:	DATE COMPLETED:
Trang Q Tran	February 5, 2010

cc: ANDA 078879
Division File
Field Copy

Endorsements:

HFD-620/TL/J.Fan/2/15/10;2/24/10
HFD-617/PM/T.Tran/2/5/10;2/24/10

F/T by: TT

V:\Chemistry Division I\Team 3\FIRMSAM\BARR\LTRS&RVS\
78879.TAtoAP.DOC

Approval

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78879	ORIG-1	BARR LABORATORIES INC	TEMOZOLOMIDE

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/s/

TRANG Q TRAN
02/24/2010

JAMES M FAN
02/24/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	078879
Drug Product Name	Temozolomide Capsules
Strength (s)	5mg, 20mg, 100mg, and 250mg
Applicant Name	Barr Laboratories, Inc.
Address	223 Quaker Road P.O. Box 2900 Pomona, NY 10970
Applicant's Point of Contact	Nicholas Tantillo
Contact's Phone Number	201-930-3650
Contact's Fax Number	201-930-3318
Submission Date(s)	Original: March 19, 2007 Telephone Amendment: August 23, 2007 Other amendments were filed that do not pertain to this review.
First Generic	Yes
Reviewer	Utpal M. Munshi, Ph.D.
Study Number (s)	7BARRP1R1GLPS34
Study Type (s)	*In vitro* permeability study
Strength(s)	N/A
Permeability Study Lab	(b) (4)
Permeability Study Lab Address	
Analytical Site	
Analytical Address	

I. EXECUTIVE SUMMARY

This is a review of dissolution data not pertaining to the BCS waiver request.

There is no USP method for this product but there is an FDA-recommended method (900 or 500 ml water with basket at 100 rpm). The firm's dissolution testing data meet the FDA specification (NLT (b) (4) (Q) in 30 min) at the S1 level. The firm's proposed specification (NLT (b) (4) (Q) in 30 min) is not acceptable. The firm should acknowledge the FDA-recommended method and specification.

The DBE will review data pertaining to the BCS waiver request later.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			X	☐	☐
Did the firm use the USP dissolution method			☐	☐	X
Did the firm use 12 units of both test and reference in dissolution testing			X	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			X	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	X	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	X
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☐	☐	X
		Plasma concentrations	☐	☐	X
	Fed BE study	PK parameters	☐	☐	X
		Plasma concentrations	☐	☐	X
	Other study	PK parameters	☐	☐	X
		Plasma concentrations	☐	☐	X
Are all eight electronic summary biotables present			☐	☐	X
Are electronic summary biotables in pdf format			☐	☐	X

NOTE: The firm provided the dissolution and formulation data in tabular format.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	Apparatus:	1 (baskets)
	Speed of Rotation:	100 rpm
	Medium:	Deaerated Water
	Volume:	900 mL
	Temperature:	37.0 +/- 0.5°C
Firm's Proposed Specifications	Q = (b) (4) Spl. time 30 min. Meets USP <711> S_1, S_2, or S_3 criteria as appropriate.	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. 2150 Perrowville Road Forest, Virginia 24551	

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) 5 min	10 min	15 min	30 min	45min	60 min	Study Report Location
ARD_RPT -2419	2/13/07	Barr -Batch Number 800104 Manufacture Date: 9/27/06	250 mg Tablet	12	Mean	35	71	88	98	99	99	Module 5.3.1.3
					Range	(b) (4)						
					RSD	38.7	14.6	4.9	1.9	2.0	1.8	
ARD_RPT -2419	2/16/07	Schering Plough Corporation, Lot # 5-PHT-14 Exp 10/2008	250 mg Tablet	12	Mean	37	78	93	99	99	99	
					Range	(b) (4)						
					% RSD	47.0	17.2	10.4	1.7	1.0	0.7	

Dissolution Conditions	**Apparatus:**	I (baskets)
	Speed of Rotation:	100 rpm
	Medium:	Deaerated Water
	Volume:	900 mL
	Temperature:	37.0 +/- 0.5°C
Firm's Proposed Specifications	Q = (b) (4) Spl. time 30 min. Meets USP <711> S_1, S_2, or S_3 criteria as appropriate.	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. 2150 Perrowville Road Forest, Virginia 24551	

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**
						5 min	**10 min**	**15 min**	**30 min**	**45min**	**60 min**	
ARD_RPT -2418	2/12/07	Barr -Batch Number 800102 Manufacture Date: 9/27/06	100 mg Tablet	12	Mean	75	97	99	100	100	100	Module 5.3.1.3
					Range	(b) (4)						
					RSD	7.0	3.2	2.6	2.0	1.7	1.7	
ARD_RPT -2418	11/17/07 11/27/06	Schering Plough Corporation, Lot # 5-DCW-33 Exp 8/2008	100 mg Tablet	12	Mean	70	97	97	98	98	98	
					Range	(b) (4)						
					RSD	27.9	24.9	23.5	19.3	15.1	10.9	

Dissolution Conditions	Apparatus:	I (baskets)
	Speed of Rotation:	100 rpm
	Medium:	Deaerated Water
	Volume:	900 mL
	Temperature:	37.0 +/- 0.5°C
Firm's Proposed Specifications	Q = (b) (4) Spl. time 30 min. Meets USP <711> S_1, S_2, or S_3 criteria as appropriate.	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. 2150 Perrowville Road Forest, Virginia 24551	

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) 5 min	10 min	15 min	30 min	45min	60 min	Study Report Location
ARD_R PT-2417	2/9/07	Barr -Batch Number 800091 Manufacture Date: 9/27/06	20 mg Tablet	12	Mean	77	100	101	101	101	101	Module 5.3.1.3
					Range	(b) (4)						
					RSD	15.3	3.2	2.6	3.0	2.8	2.8	
ARD_R PT-2417	2/15/07	Schering Plough Corporation, Lot # 5-JFL-26 Exp 8/2008	20 mg Tablet	12	Mean	85	94	93	95	97	94	
					Range	(b) (4)						
					RSD	8.2	5.4	7.1	5.2	2.9	5.7	

Dissolution Conditions	Apparatus:	1 (baskets)
	Speed of Rotation:	100 rpm
	Medium:	Deaerated Water
	Volume:	500 mL
	Temperature:	37.0 +/- 0.5°C
Firm's Proposed Specifications	Q = (b) (4) Spl. time 30 min. Meets USP <711> S_1, S_2, or S_3 criteria as appropriate.	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. 2150 Perrowville Road Forest, Virginia 24551	

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
						5 min	10 min	15 min	30 min	45min	60 min	
ARD_R PT-2416	2/8/07	Barr -Batch Number 800090 Manufacture Date: 9/27/06	5 mg Tablet	12	Mean	77	96	98	99	99	98	Module 5.3.1.3
					Range	(b) (4)						
					RSD	8.8	5.9	4.2	3.6	3.8	3.9	
ARD_R PT-2416	2/6/07	Schering Plough Corporation, Lot # 6-RPF-1 Exp 1/2009	5 mg Tablet	12	Mean	83	93	93	96	97	95	
					Range	(b) (4)						
					RSD	10.3	3.8	4.2	2.8	2.6	3.3	

II. COMMENTS:

1. The firm has requested a BCS waiver for their products and has therefore submitted *in vitro* permeability, solubility, and dissolution studies instead of *in vivo* bioequivalence data.

2. This reviewer noted the following in the original submission: 1) the dissolution data in CTD Summary Table 1 (250mg) and CTD Summary Table 3 (20mg) did not match the corresponding raw data in the *In Vitro-In Vivo* Comparative Study Reports and 2) the dissolution volume listed in CTD Summary Table 4 (5mg) did not match the corresponding volume listed in the *In Vitro-In Vivo* Comparative Study Reports. As a result, Keri Suh of the DBE contacted the firm on 8/23/07 to receive clarification on these discrepancies. In response, the firm filed a telephone amendment on 8/23/07 that contained revised CTD Summary Tables for the 250mg, 20mg, and 5mg strengths. The revised tables agree with the corresponding information in the original *In Vitro-In Vivo* Comparative Study Reports. The revised tables are included in this review. **NOTE: If the firm used dissolution volumes of 500mL for the 5mg strength and 900mL for all other strengths, then they should modify the information on p.98 of Module 5.3 accordingly.**

3. There is no USP method for this product. The firm used the method given to them by the DBE (controlled documents 06-0669 (June 2006) and 06-0737 (September 2006), recommended sampling times were 15, 30, 45, and 60 minutes)]. This method is also listed in the internal FDA dissolution database. The FDA-recommended specification in the internal database is NLT (b) (4) (Q) in 30 minutes, while the firm's recommended specification is NLT (Q) in 30 minutes. The data pass both specifications at the S1 level. Given that the firm's specification is too broad (a range of (b) (4) and that the product must be rapidly dissolving* to qualify for a BCS waiver, the DBE will ask the firm to accept a specification of NLT 85% (Q) in 30 minutes.

*NLT 85% in 30 minutes in 0.1HCl/SGF USP w/o enzymes, pH4.5 buffer, and pH 6.8 buffer/ SIF USP w/o enzymes. From the FDA Guidance: Waiver of *In Vivo* BA and BE Studies for IR Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, August 2000).

4. In addition to the dissolution data presented in this review, the firm presented two other dissolution reports: 1) dissolution comparison of Temodar 250 mg (RLD) to Barr's Temozolomide Capsules (250mg) in water, 0.1N HCl, pH 4.5 buffer, and pH 6.8 buffer and 2) dissolution comparison of 5mg, 20mg, and 100mg strength test products to the 250mg strength RLD product in deaerated water.

III. DEFICIENCY COMMENTS:

1. The firm should acknowledge the following dissolution method and specification:

Apparatus: I (basket)
Speed: 100rpm
Medium: Deaerated Water
Volume: 500mL for 5mg strength, 900mL for other strengths
Temperature: 37°±0.5°C

Specification: NLT [redacted] *(Q) in 30 minutes.*

2. If the firm in its *in vitro-in vivo* comparative studies with deaerated water used dissolution volumes of 500mL for the 5mg strength and 900mL for all other strengths, then it should modify the information on p.98 of Module 5.3 accordingly.

IV. RECOMMENDATIONS:

Based on the comments in section III above, the *in vitro* dissolution testing not pertaining to the BCS waiver request is **incomplete**.

BIOEQUIVALENCE DEFICIENCY

ANDA: 078879

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules; 5mg, 20mg, 100mg, 250mg

The Division of Bioequivalence has completed its review of The non-BCS waiver related dissolution testing portion of the submission acknowledged on the cover sheet. The review of the other studies will be conducted later. The following deficiencies have been identified:

1. Please acknowledge the following dissolution method and specification:

Apparatus: I (basket)
Speed: 100 rpm
Medium: Deaerated Water
Volume: 500mL for 5mg strength, 900mL for other strengths
Temperature: 37°±0.5°C

Specification: NLT [redacted] *(Q) in 30 minutes.*

2. If in your *in vitro-in vivo* comparative studies with deaerated water you used dissolution volumes of 500mL for the 5mg strength and 900mL for all other strengths, then please modify the information on p.98 of Module 5.3 accordingly.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

BIOEQUIVALENCE - **INCOMPLETE** Submission date: March 19, 2007

[NOTE: The *in vitro* testing is incomplete. The studies pertinent to the BCS waiver request are pending review.]

1. DISSOLUTION (Dissolution Data)	Strength: 5mg, 20mg, 100mg, 250mg Outcome: **IC**
2. Tele. Amendment (Revised dissolution data)	Strength: 5mg, 20mg, 100mg, 250mg Outcome: **IC – WC**

Outcome Decisions: **IC –Incomplete**

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/s/

Utpal Munshi
9/5/2007 05:25:24 PM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
9/6/2007 07:39:08 AM
BIOPHARMACEUTICS

Barbara Davit
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BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-879
Drug Product Name	Temozolomide Capsules
Strength(s)	5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 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 of Regulatory Affairs
Contact's Telephone Number	201-930-3650
Contact's Fax Number	201-930-3318
Original Submission Date(s)	March 19, 2007
Submission Date(s) of Amendment(s) Under Review	August 23, 2007 (Telephone Amendment-Dissolution Data) October 05, 2007 (Dissolution Acknowledgement) March 21, 2008 *(New Strengths)* April 16, 2008 *(DSI Inspection Report)* December 15, 2008 (*Telephone Amendment*)
Reviewer	Deanah L. Mitchell, Ph.D.
Study Number (s)	7BARRP1R1GLPS34
Study Type	In Vitro permeability study
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**INCOMPLETE**

REVIEW OF A BCS WAIVER & DIVISION OF SCIENTIFIC INVESTIGATIONS INSPECTION REPORT

1 EXECUTIVE SUMMARY

This application is for the ***first generic product*** of Temozolomide Capsules.
This is a review of a waiver request of in vivo bioequivalence (BE) study requirements for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg[1] and 180 mg[1] and 250 mg, along with a Division of Scientific Investigations Inspection Report (Letter Date: April

[1] 140 mg and 180 mg: Two new additional strengths were submitted on March 21, 2008 after the original submission of March 19, 2007. Located in DFS, Memo to File/First Generic and New Strength/Applications Exa/N 078879 N 000 AC 21-Mar-2008. The dissolution data for the two new additional strengths are in the Dissolution section of the current review.

16, 2008[2]) and the firm's response to Form 483 Citations. A Division of Scientific Investigations (DSI) inspection request was placed by the Office of Generic Drugs.

Review of BCS Waiver

The firm based its submission on the guidelines provided in the FDA Guidance to Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)* issued on August 2000. The reference listed drug (RLD) product is Temodar® (temozolomide) Capsules, 250 mg, by Barr Laboratories, Inc. The firm is requesting its test product be classified as BCS Class I (High Solubility-High Permeability).

The solubility data submitted does support that temozolomide is a highly soluble drug substance. The in vitro dissolution results show that the drug product (Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg[1], 180 mg[1] and 250 mg) are rapidly dissolving since greater than (b) (4) of the labeled amount of the drug substance dissolves within 30 minutes at all pH conditions tested (DFS, Review/Bioequivalence Dissolution Review/Biopharmaceutics/N 078879 N 000 19-Mar-2007). The permeability study was conducted at (b) (4). The results of the in vitro permeability study supports that Temozolomide is highly-permeable drug substance [temozolomide >>> (b) (4) (high permeability) > (b) (4) (high permeability) >> (b) (4) (low permeability)]. However, the permeability study is incomplete due to a bioanalytical deficiency and issues with the permeability study design.

On December 15, 2008, the firm submitted a telephone amendment after the DBE requested additional dissolution testing data for the 5 mg, 20 mg and 100 mg, 140 mg, 180 mg and 250 mg strengths of the test and reference products in (1) Water, (2) 0.1N HCl, (3) pH 4.5 buffer, and (4) pH 6.8 buffer using the FDA-recommended dissolution method.

The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method[3].

> On October 05, 2007 and March 21, 2008, the firm has acknowledged the FDA recommended method and specifications for its Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg.

Review of a Division of Scientific Investigations Inspection Report

The inspection report references the In Vitro Permeability Study of Temozolomide according to the Biopharmaceutical Classification System (BCS) Guidelines.

The Office of Generic Drugs (OGD) requested an inspection of the following site:

[2] DFS, Review/Review of Biopharmaceutics/Compliance Officer/N 078879 N 000 19-Mar-2007.
[3] DFS, Review/Bioequivalence Dissolution Review/Biopharmaceutics/N 078879 N 000 19-Mar-2007

Analytical Site:
(b) (4)

The inspection included In Vitro Permeability Study Report 7BARRO1R1GKOS34 and Revalidation of the Caco-2 System for BCS In Vitro Permeability Study No. 6(b) (4)BCSval.

In a letter dated April 16, 2008, the Division of Scientific Investigations (DSI) provided the Division of Bioequivalence (DBE) with its findings. Based on the inspection, the DSI provided the following conclusion:

(b) (4)

There are several deficiencies in the firm's permeability study regarding the findings during the DSI Inspection. The firm's responses to the DSI-findings are acceptable.

The waivers of in vivo BE study requirements for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, are denied at this time.

The application is **incomplete** with deficiencies.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg
Reference Product	Temodar® (temozolomide) Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg
RLD Manufacturer	Schering-Plough Corporation
NDA No.	21-029
RLD Approval Date	5 mg, 20 mg, 100 mg, 250 mg (August 11, 1999) 140 mg, 180 mg (October 19, 2006)
Indication	(b) (4) Temozolomide is indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

3.2 PK/PD Information[4]

Bioavailability	Temozolomide is rapidly and completely absorbed after oral administration. The absolute bioavailability of Temozolomide was 0.96 ±0.1, regardless of the sequence of the i.v.-p.o. or p.o.-i.v. administration, confirming that temozolomide is not subject to a marked first-pass effect[5]. See additional discussion concerning the absolute bioavailability data for Temozolomide in Section 3.11 of this review.
Food Effect	Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.
Tmax	1 hour (1.1 to 2.25 hours after a modified high-fat breakfast)
Metabolism	Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl) imidazole-4-car-boxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of

[4] External Database: DailyMed Current Medication Information. (http://dailymed.nlm.nih.gov/dailymed/about.cfm) Search: Temozolomide. Label Information. Last accessed: 10/20/08.

[5] Marzolini C,et al. Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration. Cancer Chemother Pharmacol (1998) 42(6): 433-440.

	temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.
Excretion	About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.
Half-life	Mean elimination half-life of 1.8 hours.
Drug Specific Issues (if any)	--

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:	250 mg
	Subjects:	The study should be conducted either (1) in cancer patients undergoing treatment with Temodor®; or (2) in former cancer patients who are in remission.
	Additional Comments:	Cancer patients should receive individualized regimens that use multiples of the 250 mg strength. If former cancer patients who are in remission for the BE studies, each former patient should receive a single dose of 250 mg.

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	250 mg
	Subjects:	The study should be conducted either (1) in cancer patients undergoing treatment with Temodor®; or (2) in former cancer patients who are in remission.
	Additional Comments:	Cancer patients should receive individualized regimens that use multiples of the 250 mg strength. If former cancer patients who are in remission for the BE studies, each former patient should receive a single dose of 250 mg.

Analytes to measure (in plasma/serum/blood):	Temozolomide in plasma
Bioequivalence based on:	90% CI: AUC_T, AUC_I, and C_{max}
Waiver request of in-vivo testing:	5 mg, 20 mg, 100 mg, 140 mg, and 180 mg
Source of most recent recommendations:	Controlled Correspondence No. 08-0052, submission date: January 14, 2008. \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0052.pdf

Summary of OGD or DBE History (for details, see Appendix 0):	According to the Electronic Orange Book (current through September 2008), there are no generic products currently approved for Temozolomide. Twenty eight (28) Controlled Correspondences have been submitted to the Division of Bioequivalence (DBE) requesting bioequivalence recommendations for Temozolomide capsules: One Protocol has been submitted to the DBE based on bioequivalence studies and waiver requests: • 07-063 [redacted] (b) (4) Submission Date: 09/26/07)

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	Yes	4
BCS Waivers requests	Yes	4
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	Yes	3
DSI Inspection Report	Yes	1

3.5 Data Supporting Temozolomide for a BCS Class I Drug Substance

3.5.1 Solubility Testing

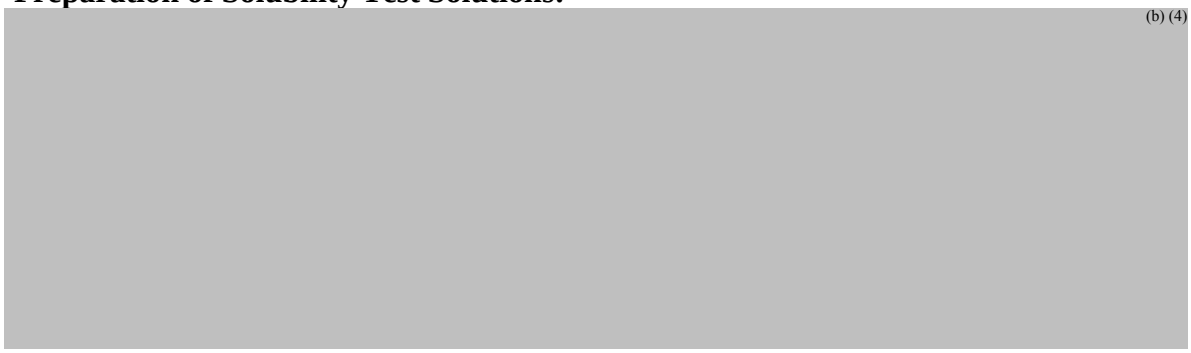
According to the FDA Guidance to Industry: *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*, issued on August 2000, a drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH ranges of 1 – 7.5. The highest marketed dosage strength of Temozolomide Capsules is 250 mg and the cutoff for solubility is 250 mg/250 mL = 1 mg/mL.

Solubility Testing:
Experimental: Solubility was determined by analyzing Temozolomide prepared in water (D.I. H_20) and four (4) different USP buffer solutions at 37 ± 1°C:

1. pH 1.2
2. pH 4.5
3. pH 6.8
4. pH 7.5

Preparation of Solubility Test Solutions:

(b) (4)



The solubility of temozolomide in different buffered media at varying pHs was carried out in triplicate. The solubility results are presented in table 1 and a graphic representation of mean pH-solubility profile was plotted.

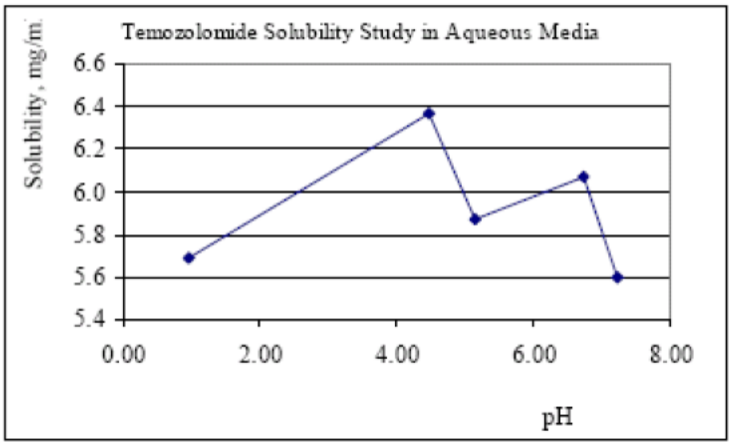
Table 1. Solubility Summary of Temozolomide in different buffered media at pH ranging from 1.2 to 7.5[6]

Media		Buffer pH1.2	Buffer pH4.5	Water	Buffer pH6.8	Buffer pH7.5
Reading before RM, pH		(b) (4)				
Reading after RM, pH	1					
	2					
	3					
	Mean	**0.95**	**4.47**	**5.14**	**6.74**	**7.22**
Solubility mg/mL	1	(b) (4)				
	2					
	3					
	Mean	**5.7**	**6.4**	**5.9**	**6.1**	**5.6**
	SD*	0.1	0.7	0.7	1.0	0.6
	CV**	0.02	0.11	0.12	0.15	0.11
Volume needed***, mL		44	39	42	41	45

*Standard deviation
**Coefficient of variation
*** to dissolve the highest dose strength (250 mg)

In Table 1, the results show that the minimum solubility of temozolomide is > 4.90 mg/mL over a pH range of 1.2 – 7.5. Therefore, it meets the criteria for designation as highly soluble drug substance.

Figure 1. A graphic plot of mean pH-solubility profile, PR6500/75.



Acceptance Criteria

- Temozolomide drug substance solubility should be not less than (NLT) (b) (4) in aqueous (buffer) solutions at 37± 1°C to be considered as highly soluble drug substance.

[6] This table is provided by the firm.

3.5.1.1 Validation of the Permeability Study

Validation Study Information

*Note: [redacted] has developed the Caco-2 cell permeability method that was used to study the permeability of temozolomide. The developed permeability system was fully validated ([redacted] Report No. 6[redacted]BCSval) prior to conducting temozolomide permeability studies.

Study No.	6[redacted]BCSval
Study Title	Revalidation of the Caco-2 System for BCS In Vitro Permeability Studies
Study Objective	To validate cell monolayer transport assays because of inter-laboratory variability in permeability results. To establish a correlation between the rank order of the permeability values obtained from the test method and the published extent of absorption data in humans using a sufficient number of test compounds spanning a range of reported human fractional absorption.
Analytical Site	[redacted]
Analytical Site Address (Permeability Lab)	
Analytical Site Address (Bioanalytical Lab)	
Radioactive Assays	
Study Dates	February 14, 2006 (Study initiation date) September 27, 2006 (Experiment completion date) February 12, 2007 (Study completion date)

Table 2. Materials and Methods for Validation of Permeability Study

Description	
Reagents & Materials	Material / Supplier / Grade (b) (4)
Cell Culture	(b) (4)
Permeability Assay Buffer (PAB)	
Quality Control of Cell Monolayers	

Following this page, 11 pages withheld in full (b)(4)

Conclusion (*according to firm)*

- Several parameters of the Caco-2 cell monolayer permeability assay were evaluated to assess the robustness of the assay for use in BCS permeability studies. Based on the results of these tests, the following conclusions can be drawn:
- The barrier properties of the Caco-2 cell monolayers are stable between days 21 and 28 post-seeding from stock cultures between passages 58 and 76 (Table 6).
- Apical efflux is present and can be inhibited by 10 μM CsA.
- The Caco-2 cell monolayer permeability method accurately identifies all twenty three test compounds as either low- or high-permeability. There is a clear correlation between the permeability coefficient of each test compound and its reported fraction absorbed in humans. Compounds with permeability coefficients in the Caco-2 monolayer assay greater than 2×10^{-6} cm/sec, have a high fraction absorbed (>90%) in humans, whereas compounds with permeability coefficients less than 1×10^{-6} cm/sec have a low fraction absorbed in humans.
- The Caco-2 cell monolayer assay is suitable for a BCS study.
- A number of test compounds showed pH-dependent permeability in the Caco-2 cell monolayer assay, including (b) (4). To minimize the occurrence of false negatives (i.e., a test compound classified as poorly permeable when it is not), it may be appropriate to run the assay using two different apical pH conditions (low pH ~ 6.5 and high pH ~ 7.4) simulating the dynamic pH environment in the intestine.

Reviewer's Comments:

- (b) (4) has developed the Caco-2 cell permeability method that was used to study the permeability of temozolomide. The permeability system was fully validated (b) (4) Report No. 6 (b) (4) BCSval) prior to conducting temozolomide permeability studies. (b) (4) also used this method to validate the permeability of (b) (4) (ANDA (b) (4)).
- The firm assessed whether the permeability of Caco-2 cell monolayers seeded from different passage numbers and the number of days in culture had any effect on the ranking order of selected 23 test compounds (in particular, (b) (4) The rank order of test compounds was consistent between days 21 and 28 post-seeding from stock cultures between passages 58 and 76.
- The BCS Guidance recommends that the *in vitro* cell culture method be validated with at least 20 model drugs ranging from low to high permeability. The firm validated the permeability study with 23 model drugs ranging from low, moderate and high permeability. The permeability studies were conducted in quadruplicate (n = 4).
- The firm evaluated possible apical efflux transport by P-glycoprotein (P-gp) of Caco-2 cell monolayers using digoxin as a substrate with and without cyclosporine A (CsA), an inhibitor of P-gp.
- In addition to the possible effects that cell passage number and days in cell culture, and the determination of efflux, the firm also evaluated whether different operators had an

effect on the permeability ranking of the reference standards by using two different operators.

- The firm provided data on the extent of absorption in humans (mean, standard deviation and coefficient of variation) fifteen (15) model drugs in the "Validation of Analytical Methods for Test Compounds, Revalidation of the Caco-2 System for BCS In Vitro Permeability Studies" (Study No. 6 (b) (4) BCSval, Date: February 12, 2007). The firm had previously validated an additional nine (9) test compounds (Study Nos. 5 (b) (4) BCSval2 and 5 (b) (4) BCSvalGLPS9).
- The firm determined the permeability coefficient, recovery, permeability class, and fraction absorbed of 23 test compounds in Caco-2 cell monolayers at two different pH values (pH 6.5 and 7.4). The test compounds established the selectivity of the Caco-2 cell monolayer assay.
- The firm estimated the linear change in receiver concentrations over time (i.e. dCr/dt) for some replicates for (b) (4) and (b) (4). The DSI Inspection noted that in Study 7BARRP1R1GLPS34, for low permeability markers, two points were used to calculate the slope instead of three when the receiver concentrations were below the limit of quantification. The firm should have a minimum of three points to calculate the slope of a line. Two out of six replicates for (b) (4) (5150 μM temozolomide) that only had one point to calculate the slope.
- The analytical method validation and revalidation of permeability assay are acceptable. Please see comments concerning the DSI inspection report.

3.6 Permeability Study (Pivotal)

3.6.1 Analytical Method Validation

Table 14. Bioanalytical Method Validation

Information Requested	Analyte 1	Internal Control	Internal Control	Internal Control
Bioanalytical method validation report location	Electronic Document Room: Section 5.3.1.1			
Study Report Number	7BARRP1R1GLPS34			
Analyte	Temozolomide			
Internal standard (IS)	--	(b) (4)		
Method description	LC/MS/MS			
Lower Limit of quantitation	0.01 µM	0.005 µM	0.005 µM	0.005 µM
% recovery (and %CV) at each concentration tested- Top well (pH 6.5)	92.9% (3.00%)			
% recovery (and %CV) at each concentration tested -Bottom well (pH 6.5)	102% (3.58%)			
Average recovery of IS (and %CV) –Top well (pH 6.5)		75.1% (7.70%)	96.0% (1.97%)	85.8% (4.73%)
Average recovery of IS (and %CV) –Bottom well (pH 6.5)		99.5% (4.69%)	101% (1.86%)	99.3% (3.36%)
Standard curve concentrations (µM)	0.005, 0.01, 0.025, 0.1, 0.25, 0.5, 0.75, 1	0.005, 0.01, 0.025, 0.1, 0.25, 0.5, 0.75, 1	0.005, 0.01, 0.025, 0.1, 0.25, 0.5, 0.75, 1	0.005, 0.01, 0.025, 0.1, 0.25, 0.5, 0.75, 1
QC concentrations (µM)	0.01 (LLOQ) 0.02 (LQC) 0.2 (MQC) 0.75 (HQC)	0.01 (LLOQ) 0.02 (LQC) 0.2 (MQC) 0.75 (HQC)	0.01 (LLOQ) 0.02 (LQC) 0.2 (MQC) 0.75 (HQC))	0.01 (LLOQ) 0.02 (LQC) 0.2 (MQC) 0.75 (HQC))
QC Intraday precision range (%)	2.57-9.31%	1.92-4.80%	3.1-8.02%	1.72-7.78%
QC Intraday accuracy range (%)	93.6-114%	94.5-108%	95.0-105%	91.4-109%
QC Interday precision range (%)	1.04-7.03%	2.06-4.42%	1.42-3.65%	4.07-5.59%
QC Interday accuracy range (%)	94.9-108%	96.3-105%	97.4-104%	94.4-104%
Bench-top stability (hrs)	4 hours @ room	4 hours @ room	4 hours @ room	4 hours @ room

	temperature	temperature	temperature	temperature
Long-term stock stability (days)	Due to the stability of Temozolomide, the pooled stock solutions (for both standards and QCs) were prepared on each run day.			
Autosampler stability (hrs)	24 hours	24 hours	24 hours	24 hours
Refrigerator stability (hrs)	24 hours	24 hours	24 hours	24 hours
Freeze-thaw stability (cycles)	The permeability samples were never frozen, therefore, no freeze-thaw stability was evaluated.			
Dilution integrity	7.5 mM diluted 10,000 fold Accuracy: 93.9% Precision: 5.78%	7.5 mM diluted 10,000 fold Accuracy: 90.6% Precision: 4.16%	7.5 mM diluted 10,000 fold Accuracy: 93.9% Precision: 1.74%	7.5 mM diluted 10,000 fold Accuracy: 95.4% Precision: 3.53%
Selectivity	No significant interferences were found			

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

Table 15. Standard Operating Procedures

SOP No.	Effective Date of SOP	SOP Title
(b) (4) 027-B	June 15, 2006	(b) (4) SOP (b) (4) 027-B. Procedure for Biopharmaceutics Classification System (BCS) Permeability Measurement.
(b) (4) 013-G	September 23, 2006	(b) (4) SOP (b) (4) 013-G. Validation of Analytical Methods for Biopharmaceutics Classification System (BCS) GLP Studies.
(b) (4) 022-D	June 25, 2006	(b) (4) SOP (b) (4) 022-E. Protocol for the Preparation of Buffers and Reagents for Permeability Measurements
(b) (4) 026-C	May 29, 2006	(b) (4) SOP (b) (4) -026-C. Procedure for Preparation of Cell Monolayers.

Reviewer's Comment:

- The firm did not provide the percent recovery of the analyte at pH 7.4, which is the pH in the basolateral compartment in the pivotal permeability study. The firm will be asked to provide the percent recovery of temozolomide at pH 7.4.
- The firm has shown the percent recovery for the internal standards ((b) (4)) at pH 6.5 and 7.4 in the Validation Study (Table 13).
- The firm did not freeze the permeability samples; therefore, freeze-thaw stability data was not evaluated.
- The submitted analytical method validation is incomplete.

Study No.	7BARRP1R1GLPS34
Study Title	In Vitro Permeability Study of Temozolomide According to the Biopharmaceutics Classification System (BCS) Guidelines Issued by the United States Food and Drug Administration
Study Objective	The objective of this study was to assess the in vitro permeability of Temozolomide using Caco-2 monolayers. The study was conducted according to the Biopharmaceutics Classification System (BCS) Guidelines issued by the United States Food and Drug Administration.
Analytical Site	(b) (4)
Analytical Site Address (Permeability Lab)	
Analytical Site Address (Bioanalytical Lab)	
Study Dates	January 24, 2007 (Study initiation date) March 02, 2007 (Experiment completion date) March 12, 2007 (Study completion date)

Table 16. Design of Permeability Study

Materials and Methods

	Description
Materials	Temozolomide, lot no. 0001001125, was supplied by Barr Laboratories, Inc. and was used for all of the studies described herein. [redacted] and [redacted] were purchased from [redacted] The permeability buffer used was pH 7.4 Hanks Balanced Salt Solution (HBSS) [redacted] to which HEPES (N-[2-Hydroxyethyl]piperazine-N,-[2-ethanesulfonic acid]) [redacted] was added at 10 mM, and D-glucose [redacted] was added at 15 mM. For HBSSg at pH 6.5, 1M of MES (2-(N-Morpholino) ethanesulfonic acid) solution was used to substitute for HEPES. Deionized water was used throughout these studies.
Analytical	All samples were assayed by LC-MS/MS using electrospray ionization. The method for the analysis of the samples was validated according to SOP [redacted]-013-G.
Cell Culture	Cell monolayers used in this study were prepared as specified in SOP [redacted] 022-D and SOP [redacted] 026-C. [redacted] Cell monolayers used for this study were from the same batch, which was certified as having properties representative of those used in the previous suitability study by measuring transepithelial electrical resistance (TEER) and Papp values of selected reference compounds.
Permeability Method & Sampling Time points	The permeability experiment was performed according to SOP [redacted]-027-B. [redacted]

	[redacted]. A summary of the experimental parameters is given below. For the A-to-B direction, samples were analyzed for Temozolomide, [redacted] and [redacted] For the B-to-A direction, samples were analyzed only for Temozolomide to demonstrate the lack of directional dependence. The reference compounds were used as permeability markers only in the A-to-B direction. Since they were not referenced in the B-to-A direction, they were not analyzed.
Experimental Parameters	Dosing Concentration: 51.5, 515, and 5150 µM of Temozolomide Internal Controls: 10 µM of [redacted] and 10 µM of [redacted] 100 µM of [redacted] Replicates: 6 Direction: A-to-B and B-to-A* (*Temozolomide only) pH: 6.5 (apical) and 7.4 (basolateral) Time Points: 15, 30, and 45 minutes for receivers and 15 and 45 minutes for donors
Data Analysis	Recovery The apparent permeability, P_{app}, and percent recovery were calculated as follows: $P_{app} = (dCr/dt) \times Vr / (A \times C_{d0})$ Percent Recovery (%) = $100 \times ((Vr \times Cr^{final}) + (Vd \times Cd^{final}))/(Vd \times C_{d0})$ Where, dCr/dt is the slope of the cumulative concentration in the receiver compartment versus time in µM s^{-1}. Vr is the volume of the receiver compartment in cm^3. A is the area of the cell monolayer (1.13 cm^2 for 12-well Transwell®). Vd is the volume of the donor compartment cm^3. Cr^{final} is the cumulative receiver concentration in µM at the end of the incubation period. Cd^{final} is the concentration in µM of the donor at the end of the incubation period. C_{d0} is the measured concentration of the 0-min donor in µM.

Stability in Permeability Assay Buffer

The chemical stability results are listed in Table 17 and 18.

Table 17. Temozolomide Stability in the Assay Buffer at pH 6.5 (n=3)

Time Point (min)	Measured Concentration (µM, Mean ± SD)	Percent Remaining (%)
0	53.9 ± 0.346	100
15	53.2 ± 2.17	98.7
45	52.3 ± 1.53	97.0

Table 18. Temozolomide Stability in the Assay Buffer at pH 7.4 (n=3)

Time Point (min)	Measured Concentration (µM, Mean ± SD)	Percent Remaining (%)
0	53.5 ± 0.231	100
15	50.4 ± 0.436	94.1
45	44.7 ± 0.265	83.5

Temozolomide is more stable in the permeability assay buffer at pH 6.5 than at 7.4. After the 45-minute incubation at 37°C, approximately 97% and 83% remained in the solution at pH 6.5 and pH 7.4.

Instability of Temozolomide in the Gastrointestinal Tract *(according to the firm)*
Temozolomide is rapidly absorbed from the GI tract. The peak plasma levels are attained in approximately an hour (Temodar labeling), which coincides with the average gastric emptying time in humans (Lui et. al. 1985[7]). The firm has studied the stability of temozolomide in simulated gastric fluid (SGF) for one hour, Simulated intestinal fluid (SIF), water, in buffers of pH 1.2, 4.5, 6.8, and 7.5 for 3 hours. Temozolomide is very stable in SGF for an hour (No loss of drug is noticed up to 1 hour). Temozolomide labeling indicates that the drug hydrolyzes to active metabolites at physiologic pH. Our results also confirm that temozolomide is not stable at pH 7.5. All sample solutions were calculated for their recovery against corresponding sample solution injected at time zero. Each instability solution was injected in duplicate. The percent recovery was plotted versus time.

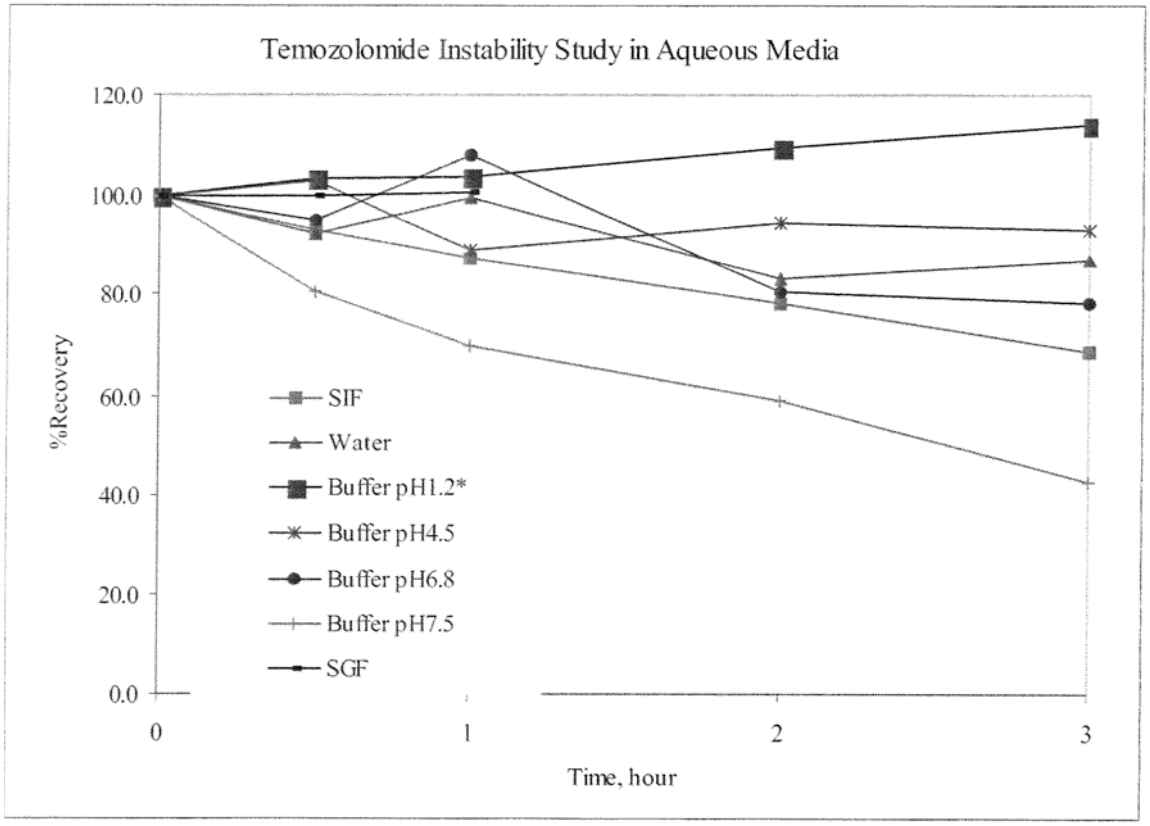
Table 19. Stability of Temozolomide in Different Media

Time, hr	SGF	SIF	Water	Buffer pH1.2	Buffer pH4.5	Buffer pH6.8	Buffer pH7.5
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
0.5	100.0	93.2	92.3	103.2	102.8	95.0	80.4
1	100.7	87.2	99.3	103.8	88.9	108.0	69.8
2		78.1	83.1	109.3	94.5	80.6	59.4
3	N/A*	68.8	86.8	114.0	92.9	78.0	42.4

(Source: Table 3, Section 6.5, Barr Report # ARD_RPT-2465)

[7] Lui et al. Comparison of Gastrointestinal pH in Dogs and Humans: Implications on the Use of the Beagle Dog as a Model for Oral Absorption in Humans. *Journal of Pharmaceutical Sciences*, Vol. 75, No. 3, 1985.

Figure 2. A graphic plot of instability profile, PR6500/74.



Firm's Analysis of Instability of Temozolomide in the Gastrointestinal Tract
However, the average intestinal pH during 2.5 hours after gastric emptying is shown to be around 6.5 (Lui et. al. 1985). Our stability studies indicate that greater than 95% of the drug remained after 1 hour and greater than 80% remained after 2 hours in the buffer of pH 6.8. This means stability of temozolomide up to 2 hours after oral dose exceeds 95% by which time most of the absorption is complete. The degradation after an hour at pH 6.8 will have a very small influence on the in vivo absorption and is not an issue in the permeability studies as the duration of these studies was only for 45 minutes.

Temozolomide Cell Permeability Study:
Permeability Results:
Each batch of the Caco-2 cell assay plates used in this study was pre-certified as having TEER values and marker compound permeabilities within specifications. The plate qualification studies also showed that these batches of Caco-2 monolayers expressed secretory transporter(s) responsible for (b) (4) B-to-A permeation, since the B-to-A Papp was much greater than the A-to-B Papp.

Table 20 presents the apparent A-to-B permeability values for the test compound, Temozolomide, and the internal reference compounds, (b) (4) and (b) (4) are shown below. All permeability experiments were conducted with six samples (n=6) to have better estimates.

Table 20. A-to-B Permeabilities of Temozolomide and Internal Control Compounds Using Caco-2 Monolayers (Mean ± SD, n = 6)

Nominal Temozolomide Dosing Concentration (µM)		51.5	515	5150
Temozolomide	P_{app} (10^{-6} cm/s)	8.49 ± 0.675	11.0 ± 2.27	7.81 ± 0.194
	Recovery (%)	90.2 ± 2.40	90.9 ± 8.71	84.9 ± 2.65
(b) (4)	P_{app} (10^{-6} cm/s)	2.40 ± 0.294	3.83 ± 0.772	3.36 ± 0.473
	Recovery (%)	91.6 ± 2.15	89.9 ± 2.00	93.5 ± 1.98
(b) (4)	P_{app} (10^{-6} cm/s)	1.93 ± 0.493	2.82 ± 0.421	2.49 ± 0.120
	Recovery (%)	88.5 ± 2.13	88.2 ± 1.45	93.2 ± 1.59
(b) (4)	P_{app} (10^{-6} cm/s)	0.216 ± 0.0536	0.274 ± 0.0450	0.178 ± 0.0328
	Recovery (%)	90.1 ± 2.82	91.6 ± 3.23	90.7 ± 2.40

Study Summary for In Vitro Permeability Study for Temozolomide Capsules, 250 mg

The recoveries of Temozolomide at all three tested concentrations were greater than 80%. The Caco-2 model can clearly discriminate low permeability compounds from high permeability compounds. The permeability rank order of the three reference compounds, (b) (4) and (b) (4), was (b) (4) > (b) (4) >> (b) (4) at all three concentrations tested. The permeability of the test compound, Temozolomide, was much higher than both of the high permeability compounds, (b) (4) and (b) (4) Because both (b) (4) and (b) (4) are at least 90% absorbed in humans, it can be inferred that Temozolomide should have a > 90% absorption in humans. The recoveries of Temozolomide at all three tested concentrations were above 80%.

The B-to-A vs. A-to-B Papp ratios for Temozolomide are summarized in Table 21.

Table 21. B-to-A vs. A-to-B P_{app} Ratios of Temozolomide (Ratios calculated using the mean P_{app} values)

Nominal Temozolomide Dosing Concentration (µM)	51.5	515	5150
A-to-B P_{app} (10^{-6} cm/s)	8.49 ± 0.675	11.0 ± 2.27	7.81 ± 0.194
B-to-A P_{app} (10^{-6} cm/s)	10.1 ± 0.381	12.6 ± 1.74	9.53 ± 3.15
B-to-A P_{app} vs. A-to-B P_{app} Ratio	1.19	1.15	1.22

Based on (b) (4) historical experience with the Caco-2 permeability assay, B-to-A vs. A-to-B Papp ratios less than 3 are not considered biologically significant. Therefore, there was no significant asymmetric flux of Temozolomide. These results showing lack of directional dependence as well as lack of concentration dependence on permeability are the evidence that Temozolomide permeates the Caco-2 membrane by passive diffusion.

Firm's Conclusions

The average Papp value for Temozolomide is greater than the Papp value of both (b) (4) and (b) (4) at all three concentrations. The B-to-A Papp to A-to-B Papp ratios of Temozolomide are less than 3 at all three concentrations. It can be concluded that Temozolomide is a highly permeable substance and could be eligible for a BCS biowaiver.

The permeability results that showed higher permeability for temozolomide compared to those of internal standards (b) (4) which were shown to have greater than 90% in vivo absorption, in conjunction with the reports that indicate greater than 90% absolute bioavailability for temozolomide (b) (4), clearly establish that temozolomide is a highly permeable drug, and therefore qualifies for a BCS waiver.

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3.7 Reviewer's Comments

1. The pivotal permeability study compared the test drug, Temozolomide, to three internal reference standards, (b) (4) (high permeability standard), (b) (4) (high permeability standard) and (b) (4) low permeability standard). The absorption of (b) (4) and (b) (4) are reported to be more than (b) (4) and (b) (4) has a fractional absorption of about 50% in humans. Therefore, if the permeability of Temozolomide is much higher than that of (b) (4) and (b) (4) then it could possibly be considered as a highly permeable drug.

2. The firm conducted the pivotal permeability study in permeability assay buffer (PAB) at two different pHs. The pH of the apical side was 6.5 and the pH of the basolateral side was 7.4. The firm should provide a detailed explanation for using two different pHs to conduct its permeability study. In addition, the firm should provide the recovery data for Temozolomide (0.01 μM) at pH 7.4.

3. The firm has concluded that there is a pH effect on some of the test compounds, including Temozolomide. The firm's studies indicated that temozolomide is more stable in the permeability assay buffer (PAB) at pH 6.8 rather than at pH 7.5. The firm conducted stability studies of temozolomide at pH buffer 6.8 and demonstrated that greater than (b) (4) of the drug remained after 1 hour and greater than (b) (4) remained after 2 hours. The firm's stability results indicate that after 1 hour of temozolomide in pH buffer 7.5, (b) (4) of Temozolomide remained after 1 hour and (b) (4) remained after 2 hours. Although the stability at pH 6.5 is shown to be more stable than 7.4, the pivotal permeability study was conducted at 10 minutes and 45-minutes, therefore, the firm concluded that after 45-minute incubation more than (b) (4) of temozolomide remained in the solution at pH 7.4.

   Note: The concentration at which the firm conducted the chemical stability studies for Temozolomide and (b) (4) are at significantly higher concentrations than the concentration used for the analytical method validation of its pivotal permeability study.

4. The firm submitted adequate chromatograms for Temozolomide (b) (4) and (b) (4) for the pivotal permeability study. There were no significant interferences found within the chromatograms.

5. The firm provided the percent (%) recovery for Temozolomide and the three reference standards: (b) (4) and (b) (4) across Caco-2 cell monolayers in the apical-to-basolateral direction (A-to-B).

(b) (4)

6. During the permeability study, the firm did not determine the permeability of the three reference standards: [redacted] and [redacted] in the basolateral-to-apical (B-to-A) direction. The firm's rationale for not performing permeability studies for the reference standards in the B-to-A direction is acceptable. Please see comments concerning the DSI inspection Findings #4 for further information.

3.8 Formulation

Location	Section 3.16, Page 45
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	--

3.9 In Vitro Dissolution

The dissolution testing was done using an FDA-recommended method (see below). The firm's dissolution testing data meet the FDA specification of NLT [redacted] (Q) in 30 minutes at the S1 level. The firm was also requested via a telephone amendment to submit additional dissolution testing data comparing all strengths 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg of Temodar (RLD) to the test product, Temozolomide Capsules, in (1) water, (2) 0.1 N HCl, (3) pH 4.5 buffer, and (4) pH 6.8 buffer. The firm submitted the requested dissolution testing on 5 mg, 20 mg, 100 mg, and 250 mg and the additional strengths of 140 mg and 180 mg. The requested dissolution testing data was acceptable.

Location of DBE Dissolution Review	Division of System Files v 2.0. Bioequivalence Dissolution Review/ Biopharmaceutics/ N 078879 N 000 19-Mar-2007.
Source of Method (USP, FDA or Firm)	FDA
Medium	Dearated Water
Volume (mL)	500 mL for 5 mg strength 900 mL for other strengths
USP Apparatus type	I (Basket)
Rotation (rpm)	100 rpm
DBE-recommended specifications	NLT [redacted] Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolved
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

3.10 Waiver Request(s)

Strengths for which waivers are requested	5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS DENIED**
If not then why?	Due to an bioanalytical deficiency

3.11 Mass Balance

According to the FDA's Guidance for Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics System, "*a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.*"

The firm did not submit any mass balance data. The RLD labeling states following a single 200 mg (70 µCi) oral dose of ^{14}C-temozolomide to 6 male cancer patients, the mean recovery of radioactivity over 7 days in urine and feces is 37.7% and 0.8% of the dose, respectively, suggesting that renal excretion is the major pathway of temozolomide elimination. This incomplete total recovery (~ 38%) may be likely due to the conversion of temozolomide to amino-imidazole-4-carboxamide (AIC), which is known to be incorporated in the biosynthesis of purines and nucleic acids. A portion of the radioactivity may also be eliminated as $^{14}CO_2$. The majority of the radioactivity is recovered in urine as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).[10]

Baker et al. reported after administering a single oral 200-mg dose of ^{14}C-temozolomide (70.2 µCi), whole blood, plasma, urine, and feces were collected from days 1-8 and on day 14. Profiles of urine samples from 0-24 hours revealed that ^{14}C-temozolomide-derived urinary radioactivity was primarily associated with unchanged drug (5.6%), AIC (12%), or 3-methyl-2,3-dihydro-4-oxoimidazol[5, 1-*d*]tetrazine-8-carxoylic acid (2.3%). The recovered radioactive dose (39%) was principally eliminated in the urine (38%), and a small amount (0.8%) was excreted in the feces. Temozolomide is converted to 5-(3-methyltriazen-l-y)imidazole-4-carboxamide (MTIC) under physiological conditions by a nonenzymatic, chemical degradation process. The conversion of temozolomide to MTIC and the further breakdown of MTIC to AIC and a methyl-diazonium cation is irreversible and pH-dependent. The oral bioavailability and plasma disposition of an early formulation of temozolomide administered as a single dose of 200-1200 mg/m^2 were

[10] NDA Review 21-029, (b) (4) (Temozolomide (Temodal®) 5 mg, 20 mg, 100 mg, and 250 mg). Clinical Pharmacology/Biopharmaceutics Review. Submission Dates: August 12, 1998, November 6, 1998, November 18, 1998.

characterized by Newlands et al[11, 12]. At the 200 mg/m^2 dose level, bioavailability of temozolomide was complete in five patients who received temozolomide both p.o. and i.v. in a crossover study design fashion; mean absolute bioavailability was 109%. [12]

Based on the above information, the recovered radioactive dose (~38%) may be incomplete due to the conversion of temozolomide to MTIC and the further breakdown to AIC. Therefore, mass balance determination for Temozolomide may not measure the actual total temozolomide amount absorbed due to its extensive conversion to MTIC and AIC, and does not provide the absolute bioavailability information for the drug.

3.12 Review of DSI Report and Firm's Response to the Form 483 Citations

The Office of Generic Drugs (OGD) requested an inspection of the Analytical Site, (b) (4) (Study Report 7BARRO1R1GKOS34 and Study No. 6 (b) (4) BCSval). DSI inspected (b) (4) between (b) (4). Following inspection of the analytical site (b) (4), a Form 483 was issued. The DSI concluded that the OGD reviewer should evaluate the following issues in terms of their impact on the outcome of Study 7BARRP1R1GLPS34: (b) (4)

(b) (4)

The firm submitted its response to the Form 483 citations.

(b) (4)

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(b) (4)

3.13 Deficiency Comments

1. During the Permeability study No. 7BARRP1R1GLPS34, the firm conducted the study using two different pHs. For the apical compartment the pH was 6.5 and for the basolateral compartment the pH was 7.4. The firm should provide a detailed justification for using the two different pHs to conduct its permeability study.

2. During the Permeability study No. 7BARRP1R1GLPS34, the pH of the apical compartment (top well) was 6.5 and the pH of the basolateral compartment (bottom well) was 7.4. The firm provided the percent recovery in the top and bottom wells

(b) (4)

at pH 6.5. The firm should provide a detailed explanation for using two different pHs to conduct its permeability study. In addition, the firm should provide the percent recovery of temozolomide (0.01 µM) in the basolateral compartment at pH 7.4.

3. For future submissions, the firm should establish an acceptable criteria (including data points, linearity) for estimating rate of change of receiver concentration (*dCr/dt*) for estimating apparent permeability (*Papp*). The firm should use a minimum of three points to calculate the slope of the line for low, medium, and high permeability drug substances.

4. For future submissions, the firm should establish an acceptable criteria for reporting percent recovery for permeability experiments in their Standard Operating Procedures (SOPs).

3.14 Recommendations

1. The Division of Bioequivalence accepts the *in vitro* solubility study, Report No. MHT-826 conducted by the Barr Laboratories, Inc. on its Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, Lot. No. 0001001125. Temozolomide is a highly soluble drug substance.

2. The Division of Bioequivalence finds the *in vitro* permeability study, Report No. 7BARRP1R1GLPS34 on its Temozolomide, Lot No. 0001001125 is incomplete due to the deficiencies mentioned above.

3. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing conducted by Barr Laboratories, Inc. on its Temozolomide Capsules, 5 mg (Batch No. 800090), 20 mg (Batch No. 800091), 100 mg (Batch No. 800102), 140 mg (Batch No. 800232), 180 mg (Batch No. 800235), and 250 mg (Batch No. 800104) demonstrated that this drug product is rapidly dissolving.

4. The dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL (for 5 mg strength) and 900 mL (for other strengths) of Dearated Water at 37ºC + 0.5ºC using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification(s):

   NLT (b) (4) (Q) of temozolomide dissolved in 30 minutes.

The firm should be informed of the above deficiencies and recommendations.

3.15 Comments for Other OGD Disciplines

Discipline	Comment
Bio PM	From the bioequivalence standpoint, the firm's responses to the DSI-findings are acceptable. No further action is necessary.

3.16 Formulation Data[16]

Ingredients	Code	Strength (mg/capsule)					
Temozolomide	(b) (4)	5	20	100	140	180	250
Anhydrous Lactose, NF (b) (4)		(b) (4)					
Sodium Starch Glycolate, NF (b) (4)							
Tartaric Acid, NF (b) (4)							
POVIDONE, USP (b) (4)							
Colloidal Silicon Dioxide, NF (b) (4) (b) (4)							
Stearic Acid, NF							
Size #3 capsule shells (Cap and Body: Off White Opaque; Ink: Green; Imprint: barr 1078 5 mg		Size#3					
Size #2 capsule shells (Cap and Body: Off White Opaque; Ink: Brown; Imprint: barr 1077 20 mg			Size#2				
Size #1 capsule shells (Cap and Body: Off White Opaque; Ink: Blue; Imprint: barr 1076 100 mg				Size#1			
Size #0 capsule shells with blue opaque cap and off-white opaque body; Ink: Black; Imprint: barr 1159 140 mg					Size#0		
Size #0 capsule shells with dark orange opaque cap and off-white opaque body; Ink: Black; Imprint: barr 1160 180 mg						Size#0	
Size #0 capsule shells (Cap and Body: Off White Opaque; Ink: Black; Imprint: barr 1075 250 mg							Size#0
Total Capsule Fill Weight (mg)		**180**	**180**	**180**	**252**	**324**	**450**

(b) (4)

[16] ANDA 78-879 (Submission date: 03-19-07). Formulation and IIG Excipient Data. **\\FDSWA150\NONECTD\N78879\N_000\2007-03-19 (Module 2 and 5).**

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Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	NO
Comments on the drug product formulation:	None of the inactive ingredients exceed the FDA's Inactive Ingredient Guide limits for Approved Drug Products. There are several color additives in the ink of the gelatin capsule that contain elemental iron: Green (b) (4) Brown (b) (4) and Black (b) (4) The amount of elemental iron in all strengths is less than the CFR's daily limit of 5 mg/day. The amount of elemental iron in the test product is in accordance with 21 § CFR 73.1200 (c).

Firm's Comments:

The capsules of the 5 mg, 20 mg, and 100 mg strengths are dose-similar and the 100 mg, 140 mg, 180 mg, and 250 mg strengths are dose-proportional.

Reviewer's Comments:

The firm may request a waiver of in vivo BE testing for the lower strengths, if BE studies on the highest strength are acceptable, the lower strengths are formulated in proportion to the highest strengths and dissolution testing on all strengths is acceptable.

Although the RLD formulation's lack proportionality among the different strengths, biowaivers may be granted because[17]:

1. Temozolomide dissolves rapidly with all the strengths of the RLD meeting the specification of not less than (b) (4) within 30 minutes. The observation of linear oral availability of temozolomide over the dose range of 500 mg/m^2 to 1000 mg/m^2 suggests that there is no dissolution-limited absorption at doses as high as 1000 mg/m^2. Therefore, it is acceptable to dose as high as 1000 mg/m^2 in the individualized dosing regimens for BE studies.
2. Temozolomide has good aqueous solubility, 3.1 mg/ml in water, 3.2 mg/ml in 0.901 M HCl, and 3.1 mg/ml in pH 6.9 phosphate buffer.
3. The Tmax of temozolomide is approximately 1 hr for a dose as high as 750 mg/m^2, indicating that the in-vivo release and absorption of temozolomide from capsules is rapid.

[17] Controlled Correspondence # 04-1047 (v:\\firmsnz\(b) (4)\controls\041047C1204.doc)

3.17 Dissolution Data

Dissolution Review Path	DFS, Review/Bioequivalence Dissolution Review/Biopharmaceutics/N 078879 N 000 19-Mar-2007

Table 24. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP Apparatus I (Basket)
	Speed of Rotation:	100 rpm
	Medium:	Dearated Water
	Volume:	900 mL (for 20, 100, 140 mg, 180 mg and 250 mg strengths 500 mL (for 5 mg strength only)
	Temperature:	37.0 ± 0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) in 30 minutes	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. 2150 Perrowville Road Forest, Virginia 24551	

Table 25. Dissolution Comparison of Temodar 250 mg and Barr's Temozolomide Capsules, 250 mg in Dearated Water (FDA-Recommended Method)

Dosage Unit	Brand Lot: 5-PHT-14 (PR6435/107)						Barr Lot: 800104 (PR6435/112)					
	% Dissolved											
	5 min	10 min	15 min	30 min	45 min	60 min	5 min	10 min	15 min	30 min	45 min	60 min
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	37	78	93	99	99	99	35	71	88	98	99	99
Max	(b) (4)											
Min												
%RSD	47.0	17.2	10.4	1.7	1.0	0.7	38.7	14.6	4.9	1.9	2.0	1.8

Table 26. Dissolution Comparison Between Temodar 250 mg and Barr's Temozolomide Capsules, 250 mg in 0.1 N HCl

Dosage Unit	Barr Lot: 800104 (PR6500/21)				Brand Lot: 5-PHT-14 (PR6500/51)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	100	101	100	100	95	100	100	100
Max	(b) (4)							
Min								
%RSD	1.5	1.8	1.7	1.8	5.6	1.9	1.8	1.7

Table 27. Dissolution Comparison Between Temodar 250 mg and Barr's Temozolomide Capsules, 250 mg in Buffer pH 4.5

Dosage Unit	Barr Lot: 800104 (PR6500/62)				Brand Lot: 5-PHT-14 (PR6500/45)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	98	101	101	101	99	100	100	99
Max	(b) (4)							
Min								
%RSD	4.7	2.6	2.4	2.6	2.4	2.1	2.0	1.7

Table 28. Dissolution Comparison Between Temodar 250 mg and Barr's Temozolomide Capsules, 250 mg in Buffer pH 6.8

Dosage Unit	Barr Lot: 800104 (PR6595/10)				Brand Lot: 5-PHT-14 (PR6434/77)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	94	94	90	88	96	94	92	89
Max	(b) (4)							
Min								
%RSD	2.3	1.7	1.7	2.1	1.4	1.0	1.0	0.8

Table 29. Dissolution Comparison Between Temodar 180 mg and Barr's Temozolomide Capsules, 180 mg in Dearated Water (FDA-Recommended Method)

Sample #	Temozolomide Capsules, 180 mg Batch # 800235						Temodar (Temozolomide) Capsules, 180 mg Lot # 7TDR004					
	% Dissolved											
	5 min	10 min	15 min	30 min	45 min	60 min	5 min	10 min	15 min	30 min	45 min	60 min
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	**49**	**91**	**96**	**98**	**99**	**99**	**53**	**90**	**97**	**98**	**98**	**98**
Min	(b) (4)											
Max												
% RSD	**41.2**	**7.7**	**4.4**	**1.6**	**1.6**	**1.6**	**16.2**	**3.3**	**1.3**	**1.0**	**1.0**	**1.0**
Ref.	PR6636/53						PR6503/110-115					
Test Date	01/28/08						01/30/08					

Table 30. Dissolution Comparison Between Temodar 180 mg and Barr's Temozolomide Capsules, 180 mg in 0.1 N HCl

Dosage Unit	Barr Lot: 800235 (PR8103/20)				Brand Lot: 7TDR008 (PR8103/20)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	99	100	100	99	102	102	102	101
Max	(b) (4)							
Min								
%RSD	3.4	2.2	2.3	2.4	1.9	1.8	1.5	2.7

Table 31. Dissolution Comparison Between Temodar 180 mg and Barr's Temozolomide Capsules, 180 mg in Buffer pH 4.5

Dosage Unit	Barr Lot: 800235 (PR8111/35)				Brand Lot: 7TDR008 (PR8111/35)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	100	100	101	101	99	101	101	101
Max	(b) (4)							
Min								
%RSD	4.5	3.4	2.1	2.0	1.6	0.9	0.9	1.1

Table 32. Dissolution Comparison Between 180 mg and Barr's Temozolomide Capsules, 180 mg in Buffer pH 6.8

Dosage Unit	Barr Lot: 800235 (PR8103/51)				Brand Lot: 7TDR008 (PR8103/51)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	92	94	90	87	97	96	91	90
Max	(b) (4)							
Min								
%RSD	8.0	2.3	2.6	2.6	2.6	1.4	1.1	1.8

Table 33. Dissolution Comparison Between Temodar 140 mg and Barr's Temozolomide Capsules 140 mg in Dearated Water (FDA-Recommended Method)

Sample #	Temozolomide Capsules, 140 mg Batch # 800232						Temodar (Temozolomide) Capsules, 140 mg Lot # 6TEM003					
	% Dissolved											
	5 min	10 min	15 min	30 min	45 min	60 min	5 min	10 min	15 min	30 min	45 min	60 min
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	49	82	97	99	99	98	57	88	96	98	98	98
Min	(b) (4)											
Max												
% RSD	53.5	20.9	3.5	1.8	1.6	1.9	14.1	8.1	2.9	0.8	0.8	1.0
Ref.	PR6503/100-105						PR6636/45					
Test Date	01/16/08						01/31/08					

Table 34. Dissolution Comparison Between Temodar 140 mg and Barr's Temozolomide Capsules 140 mg in 0.1 N HCl

Dosage Unit	Barr Lot:800232 (PR8111/16)				Brand Lot: 7TEM039 (PR8111/16)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	99	99	100	100	101	101	101	101
Max	(b) (4)							
Min								
%RSD	2.8	3.2	2.8	2.6	1.2	1.1	1.3	1.1

Table 35. Dissolution Comparison Between Temodar 140 mg and Barr's Temozolomide Capsules 140 mg in Buffer pH 4.5

Dosage Unit	Barr Lot:800232 (PR8111/54)				Brand Lot: 7TEM039 (PR8111/54)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	101	101	101	100	98	100	100	100
Max	(b) (4)							
Min								
%RSD	2.4	2.4	2.3	2.0	2.4	1.0	0.9	1.0

Table 36. Dissolution Comparison Between Temodar 140 mg and Barr's Temozolomide Capsules 140 mg in Buffer pH 6.8

Dosage Unit	Barr Lot: 800232 (PR8103/88)				Brand Lot: 7TEM039 (PR8103/88)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	98	95	93	90	97	96	92	89
Max	(b) (4)							
Min								
%RSD	3.0	1.9	1.6	1.7	1.4	1.5	1.3	1.5

Table 37. Dissolution Comparison Between Temodar 100 mg and Barr's Temozolomide Capsules 100 mg in Dearated Water (FDA-Recommended Method)

Sample #	Temozolomide Capsules, 100 mg Batch # 800102						Temodar (Temozolomide) Capsules, 100 mg Lot # 5-DCW-33					
	% Dissolved											
	5 min	10 min	15 min	30 min	45 min	60 min	5 min	10 min	15 min	30 min	45 min	60 min
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	75	97	99	100	100	100	70	97	97	98	98	98
Min	(b) (4)											
Max												
% RSD	7.0	3.2	2.6	2.0	1.7	1.7	27.9	24.9	23.5	19.3	15.1	10.9
Ref.	PR6434/129						PR6434/130					
Test Date	02/12/07						11/17/2006 & 11/27/06					

Table 38. Dissolution Comparison Between Temodar 100 mg and Barr's Temozolomide Capsules 100 mg in 0.1 N HCl

Dosage Unit	Barr Lot: 800102 (PR8105/08-11)				Brand Lot: 7RSA060 (PR8108/9-12)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	101	101	102	102	102	103	102	103
Max	(b) (4)							
Min								
%RSD	3.0	2.8	3.0	2.9	2.0	1.9	1.6	1.9

Table 39. Dissolution Comparison Between Temodar 100 mg and Barr's Temozolomide Capsules 100 mg in Buffer pH 4.5

Dosage Unit	Barr Lot: 800102 (PR8111/73)				Brand Lot: 7RSA060 (PR8111/73)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	100	101	101	101	100	101	101	101
Max	(b) (4)							
Min								
%RSD	5.0	3.4	3.5	3.5	2.3	2.2	2.0	2.0

Table 40. Dissolution Comparison Between Temodar 100 mg and Barr's Temozolomide Capsules 100 mg in Buffer pH 6.8

Dosage Unit	Barr Lot: 800102 (PR8109/47-50)				Brand Lot: 7RSA060 (PR8103/58-60)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	98	96	93	90	98	96	92	90
Max	(b) (4)							
Min								
%RSD	2.4	2.7	2.4	2.7	2.1	2.4	2.2	2.4

Table 41. Dissolution Comparison Between Temodar 20 mg and Barr's Temozolomide Capsules 20 mg in Dearated Water (FDA-Recommended Method)

Sample #	Temozolomide Capsules, 20 mg Batch # 800091						Temodar (Temozolomide) Capsules, 20 mg Lot # 5-JFL-26					
	% Dissolved											
	5 min	10 min	15 min	30 min	45 min	60 min	5 min	10 min	15 min	30 min	45 min	60 min
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	77	100	101	101	101	101	85	94	93	95	97	94
Min	(b) (4)											
Max												
% RSD	15.3	3.2	2.6	3.0	2.8	2.8	8.2	5.4	7.1	5.2	2.9	5.7
Ref.	PR6435/102						PR6435/109					
Test Date	02/09/06						02/15/07					

Table 42. Dissolution Comparison Between Temodar 20 mg and Barr's Temozolomide Capsules 20 mg in 0.1 N HCl

Dosage Unit	Barr Lot: 800091 (PR8105/19-22)				Brand Lot: 7NCW045 (PR8108/22-25)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	102	102	102	102	99	99	99	99
Max	(b) (4)							
Min								
%RSD	2.5	2.4	2.4	2.4	0.9	1.0	1.0	1.0

Table 43. Dissolution Comparison Between Temodar 20 mg and Barr's Temozolomide Capsules 20 mg in Buffer pH 4.5

Dosage Unit	Barr Lot: 800091 (PR8108/37-40)				Brand Lot: 7NCW045 (PR8108/41-44)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	100	100	100	100	99	100	100	100
Max	(b) (4)							
Min								
%RSD	2.3	2.2	2.2	2.3	0.7	0.6	1.1	0.7

Table 44. Dissolution Comparison Between Temodar 20 mg and Barr's Temozolomide Capsules 20 mg in Buffer pH 6.8

Dosage Unit	Barr Lot: 800091(PR8103/73)				Brand Lot:7NCW0450 (PR8103/73)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	93	91	88	86	95	92	88	84
Max	(b) (4)							
Min								
%RSD	4.8	4.7	4.3	4.0	1.0	1.0	1.0	1.0

Table 45. Dissolution Comparison Between Temodar 5 mg and Barr's Temozolomide Capsules 5 mg in Dearated Water (FDA-Recommended Method)

Sample #	Temozolomide Capsules, 5 mg Batch # 800090						Temodar (Temozolomide) Capsules, 5 mg Lot # 6-RPF-1					
	% Dissolved											
	5 min	10 min	15 min	30 min	45 min	60 min	5 min	10 min	15 min	30 min	45 min	60 min
1	(b) (4)											
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
Mean	77	96	98	99	99	98	83	93	93	96	97	95
Min	(b) (4)											
Max												
% RSD	8.8	5.9	4.2	3.6	3.8	3.9	10.3	3.8	4.2	2.8	2.6	3.3
Ref.	PR6435/98						PR6435/94					
Test Date	02/08/07						02/06/07					

Table 46. Dissolution Comparison Between Temodar 5 mg and Barr's Temozolomide Capsules 5 mg in 0.1 N HCl

Dosage Unit	Barr Lot:800090 (PR8109/08-11)				Brand Lot: 8HLO005 (PR8104/27-30)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	98	98	98	98	98	98	98	98
Max	(b) (4)							
Min								
%RSD	2.9	3.0	2.6	2.9	2.1	1.8	1.8	1.9

Table 47. Dissolution Comparison Between Temodar 5 mg and Barr's Temozolomide Capsules 5 mg in Buffer pH 4.5

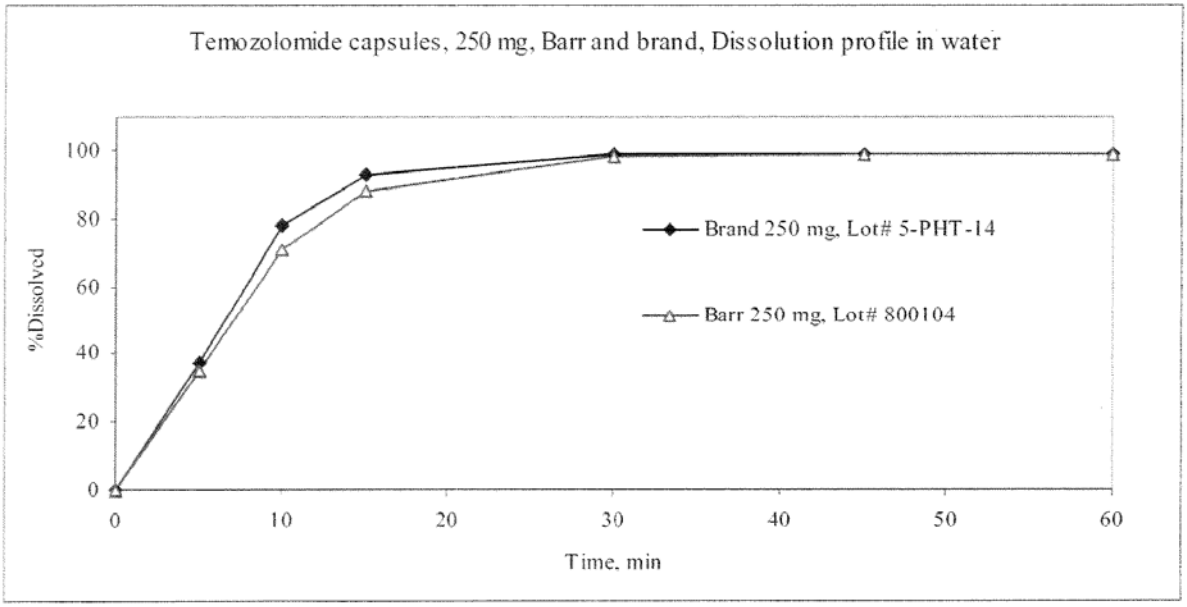
Dosage Unit	Barr Lot: 800090 (PR8109/20-23)				Brand Lot: 8HLO005 (PR8111/56-58)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	99	99	99	99	96	96	96	96
Max	(b) (4)							
Min								
%RSD	5.0	5.2	5.1	5.1	2.2	2.1	2.0	2.1

Table 48. Dissolution Comparison Between Temodar 5 mg and Barr's Temozolomide Capsules 5 mg in Buffer pH 6.8

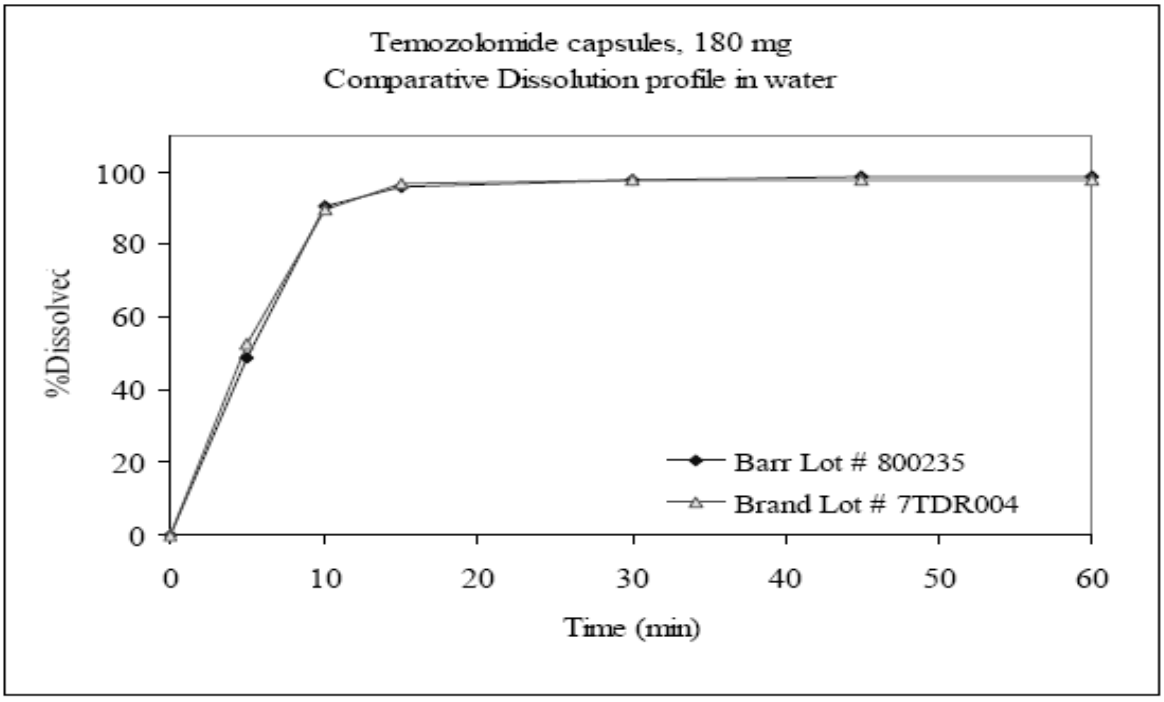
Dosage Unit	Barr Lot: 800090 (PR8105/35-38)				Brand Lot: 8HLO005 (PR8105/39-42)			
	% Dissolved							
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	93	91	88	86	92	90	87	85
Max	(b) (4)							
Min								
%RSD	4.6	4.7	4.4	3.8	1.3	1.3	1.3	1.4

Dissolution Profiles (FDA-recommended method only)

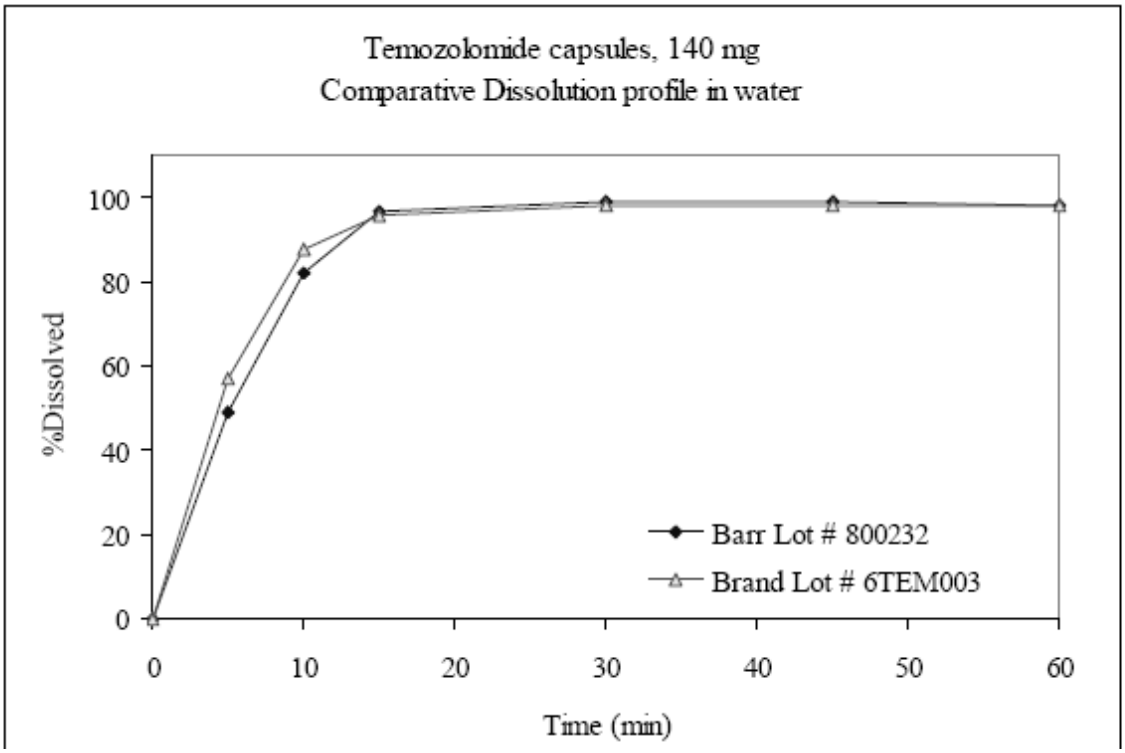
A. 250 mg strength tablets



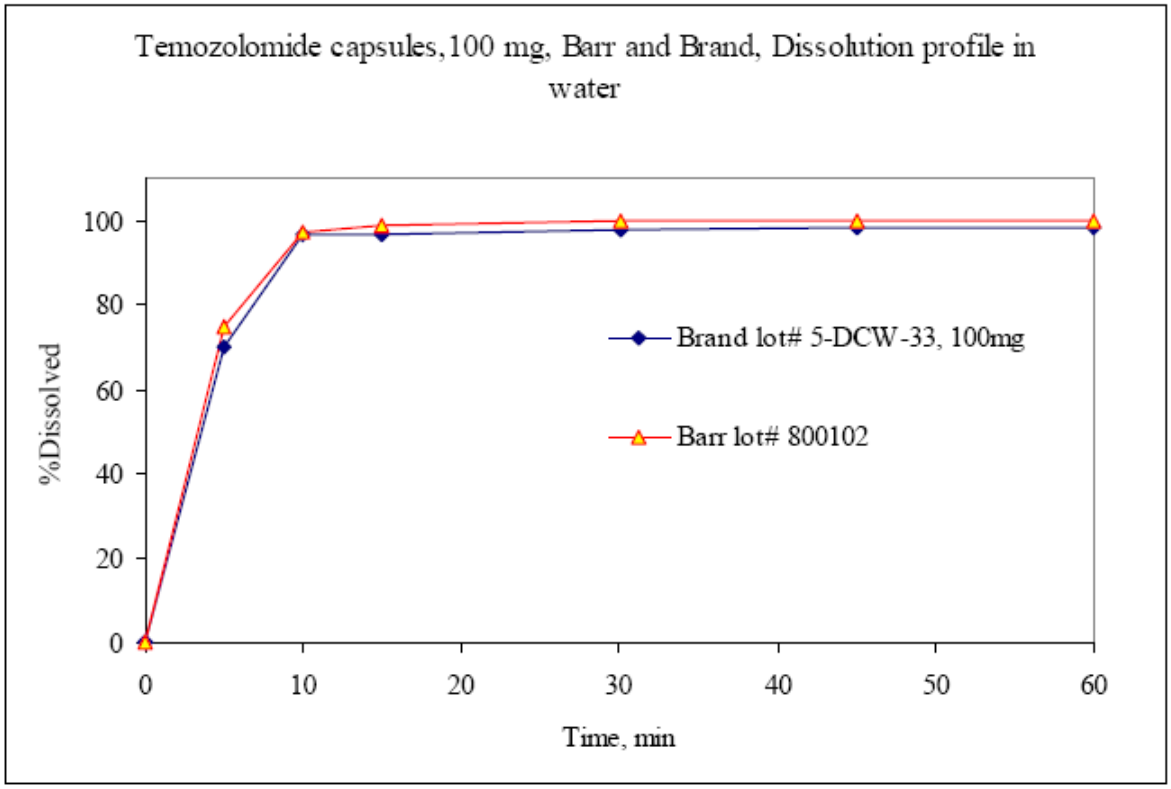
B. 180 mg strength tablets



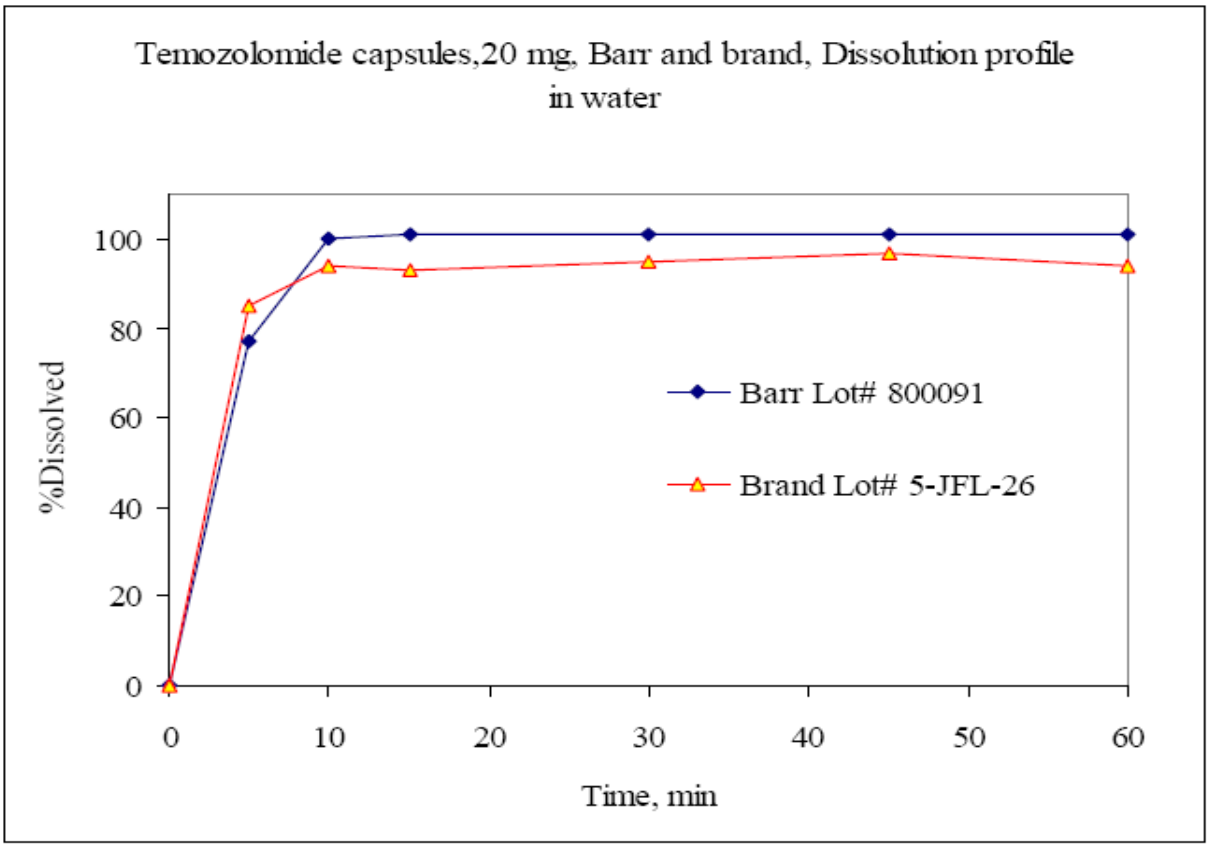
C. 140 mg strength tablets



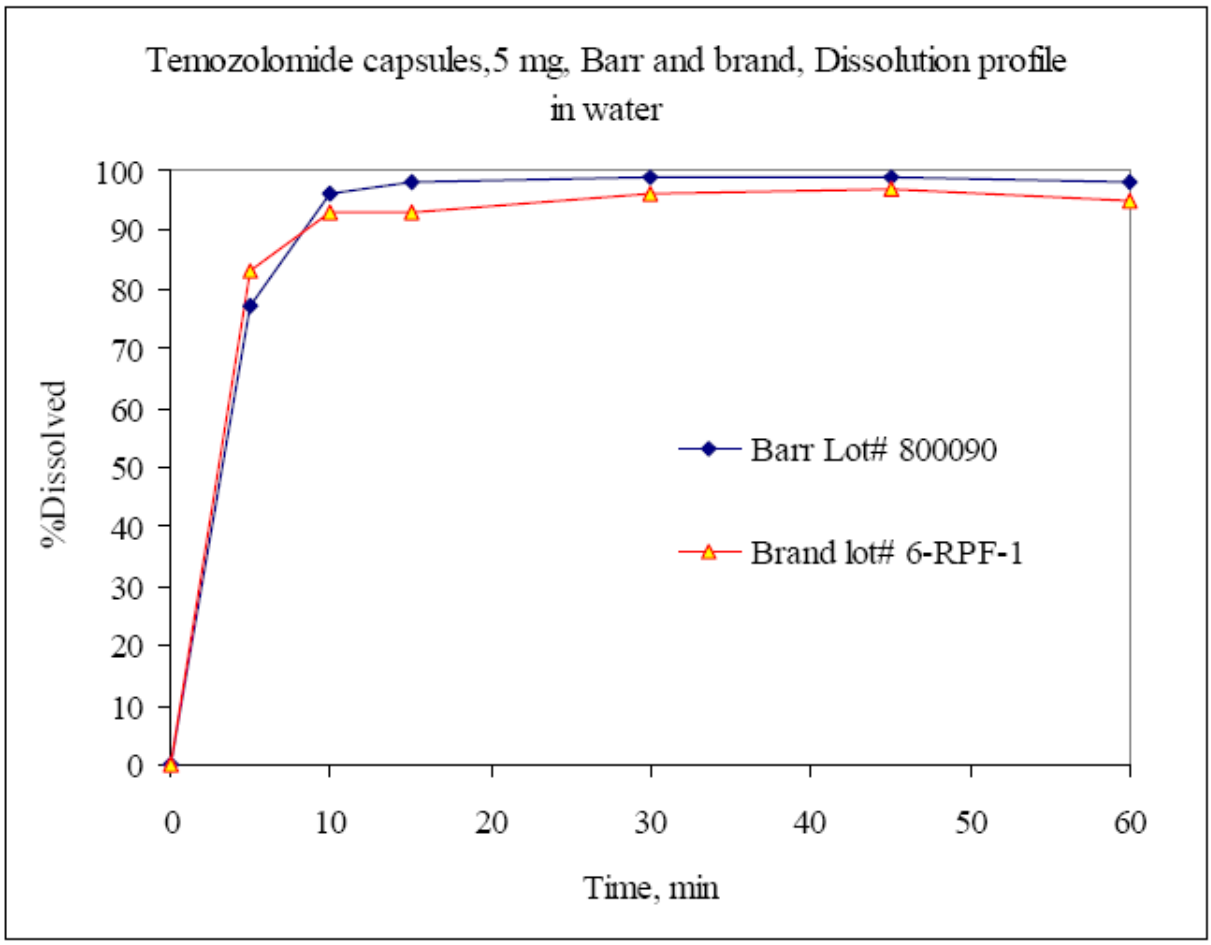
D. 100 mg strength tablets



E. 20 mg strength tablets



F. 5 mg strength tablets



3.18 Detailed Regulatory History

None.

3.19 Consult Reviews

None.

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3.22 Additional Attachments

Division of Scientific Investigation (DSI) Inspection Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 16, 2008

TO: Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence (HFD-650)

FROM: Sriram Subramaniam, Ph.D.
Xikui Chen, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. 4/16/08
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering ANDA 78-879, Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg, Sponsored by Barr Laboratories

At the request of the Office of Generic Drug (OGD), Division of Bioequivalence (DBE), the Division of Scientific Investigations audited the following *in vitro* permeability studies, submitted as part of biopharmaceutical classification system (BCS) biowaiver.

Report 7BARRP1R1GLPS34:	In Vitro Permeability Study of Temozolomide According to the Biopharmaceutical Classification System (BCS) Guidelines Issued by the United States Food and Drug Administration
Report 7BARRP1R1GLPS34 (Appendix 1):	Validation of an LC/MS Method for Temozolomide Permeability Samples, SOP (b) (4) -013-G
Study 6 (b) (4) BCSval:	Revalidation of the Caco-2 System for BCS *In Vitro* Permeability Studies

The *in vitro* studies were submitted to support a biowaiver **request in accordance with CDER's BCS guidance***. **The** guidance allows biowaivers for immediate-release oral dosage forms that exhibit **high** solubility and **high** permeability with **rapid** dissolution (i.e. Class I drug).

The *in vitro* permeability study and the associated validation studies were conducted at (b) (4) (b) (4). Caco-2 cell monolayers were used to assess the apparent permeability (Papp) of temozolomide.

A Form 483 was issued to (b) (4) at the conclusion of the inspection (b) (4). Our evaluation of the significant findings and the firm's response follows:

1. (b) (4)

2.

* CDER's Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutical Classification System. (August 2000)

Following this page, 2 pages withheld in full (b)(4)

3. (b) (4)

4.

5.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Xikui Chen, Ph.D.

Sriram Subramaniam, Ph.D.

Final Classification:
VAI – (b) (4).

cc:
HFD-45/RF
HFD-45/Vaccari
HFD-48/Subramaniam/Chen/ Himaya/CF
HFD-650/Munshi/Suh
HFR-CE1505/Despins
Draft: XC 2/26/08
Edit: SS 3/27/08
DSI: (b) (4); O:\BE\EIRCOVER\78879bar tem doc
FACTS ID: (b) (4)

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-879

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. For your Permeability Study (Study Report No. 7BARRP1R1GLPS34), the pH of the apical compartment (top well) was 6.5 and the pH of the basolateral compartment (bottom well) was 7.4. Please provide a detailed justification for using two different pHs to conduct your permeability study.

2. Also, in your Permeability Study report (Study Report No. 7BARRP1R1GLPS34), you provided the percent recovery in the top and bottom wells at pH 6.5 for Temozolomide. However, you did not provide the percent recovery of Temozolomide (0.01 µM) in the top and bottom wells at pH 7.4. Therefore, please submit the percent recovery (and % coefficient of variation) of Temozolomide (0.01 µM) at pH 7.4.

3. For future submissions, please establish acceptable criteria (including number of data points used in the linearity regression) for estimating rate of change of receiver concentration (*dCr/dt*) in the calculation of the apparent permeability (*Papp*). Please use a minimum of three points to calculate the slope of the line for low, medium, and high permeability drug substances.

4. For future submissions, please establish acceptable criteria for reporting percent recovery for permeability experiments in your Standard Operating Procedures (SOPs).

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

3.23 Outcome Page

ANDA: 78-879

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7267	3/19/2007	Other	BCS Waiver	1	1
7267	3/19/2007	Other	BCS Waiver	1	1
7267	3/19/2007	Other	BCS Waiver	1	1
7267	3/19/2007	Other	BCS Waiver	1	1
7267	3/19/2007	Bioequivalence Study	In-Vitro Study (Nasal, Binding)	1	1
7267	3/19/2007	Bioequivalence Study	In-Vitro Study (Nasal, Binding)	1	1
7267	3/21/2008	Other	BCS Waiver	1	1
7267	3/21/2008	Other	BCS Waiver	1	1
7267	8/23/2007	Other	Study Amendment Without Credit (WC)	0	0
7267	10/5/2007	Other	Study Amendment Without Credit (WC)	0	0
7267	12/15/2008	Other	Study Amendment Without Credit (WC)	0	0
7267	4/16/2008	Other	DSI Inspection Report	1	1
				Bean Total:	9

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

/s/

Deanah L Mitchell
1/14/2009 08:29:37 AM
BIOPHARMACEUTICS

April Braddy
1/15/2009 12:51:49 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
1/16/2009 09:34:45 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-879
Drug Product Name	Temozolomide Capsules
Strength(s)	5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg
Applicant Name	Barr Laboratories, Inc.
Address	225 Summitt Avenue
Applicant's Point of Contact	Nicholas Tantillo, Sr. Director Regulatory Affairs
Contact's Telephone Number	201-930-3650
Contact's Fax Number	201-930-3318
Original Submission Date(s)	March 19, 2007
Submission Date(s) of Amendment(s) Under Review	February 06, 2009
Reviewer	Deanah L. Mitchell, Ph.D.
Study Number (s)	7BARRP1R1GLPS34
Study Type (s)	In Vitro Permeability Study
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**ACCEPTABLE**

Review of a Bioequivalence Amendment

1 EXECUTIVE SUMMARY

This is a review of a bioequivalence amendment.

On March 19, 2007, Barr Pharmaceuticals submitted an application for the *first generic* product of Temozolomide Capsules. In the application the firm requested waivers of in vivo bioequivalence (BE) study requirements for its Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg. The firm based its submission on the guidelines provided in the FDA Guidance to Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)* issued on August 2000. The reference listed drug (RLD) product is Temodar® (temozolomide) Capsules, 250 mg, by Schering-Plough Corporation.

On January 27, 2009[1], a deficiency letter was issued to the firm asking them to provide (1) detailed justification for using two different pHs to conduct the permeability study, (2) to provide the percent recovery and % coefficient of variation of Temozolomide (0.01μM) at pH 7.4, and (3) in the future to establish an acceptable criteria for estimating rate of change of receiver concentration and to establish an acceptable criteria for reporting percent recovery for permeability experiments in their Standard Operating Procedures (SOPs). The firm responded with an explanation to justify the deficiencies (dated February 06, 2009). The firm's responses are acceptable.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

All BCS Committee members are in agreement that Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg should be classified as a BCS Class I drug, see Additional Attachments I section of the review for meeting minutes.

The application is considered **acceptable**.

[1] DFS, Review/Bioequivalence Review/N 078879 N 000 AB 15-Dec-2008

2 TABLE OF CONTENTS

3 RESPONSE TO DEFICIENCY

(Letter Date: 01/27/09)

DBE Comment 1:

For your Permeability Study (Study Report No. 7BARRP1R1GLPS34), the pH of the apical compartment (top well) was 6.5 and the pH of the basolateral compartment (bottom well) was 7.4. Please provide a detailed justification for using two different pHs to conduct your permeability study.

Firm's Response to Comment 1:

The data to address this request were already included in our Abbreviated New Drug Application dated March 19, 2007 and subsequent amendment dated March 21, 2008. As per your request, a detailed justification is provided using the information that was included in our ANDA.

(b) (4)

Following this page, 1 page withheld in full (b)(4)

DBE Comment 2:

Also, in your Permeability Study report (Study Report No. 7BARRP1R1GLPS34), you provided the percent recovery in the top and bottom wells at pH 6.5 for Temozolomide. However, you did not provide the percent recovery of Temozolomide (0.01 μM) in the top and bottom wells at pH 7.4. Therefore, please submit the percent recovery (and % coefficient of variation) of Temozolomide (0.01 μM) at pH 7.4.

Firm's Response to Comment 2:

The percent recoveries of Temozolomide from the top and bottom wells were determined at both pH 6.5 and pH 7.4 and the data were submitted in our Permeability Study report (Study Report No. 7BARRP1R1GLPS34).

At pH 6.5, the recoveries were 92.9± 3.00% and 102 ± 3.58% from the top and bottom chambers, respectively. At pH 7.4, the recoveries were 84.7 ± 2.30% and 92.3± 2.39% from the top and bottom chambers, respectively.

Please note that the recoveries results of Temozolomide from the top and bottom wells were included in Tables A10 and A11, which was located on pages 33 and 34 of Study Report No. 7BARRP1R1GLPS34 (see Module 5.3, pages 47 and 48 of our Abbreviated New Drug Application dated March 19, 2007 for additional details).

DBE Comment 3:

For future submissions, please establish acceptable criteria (including number of data points used in the linearity regression) for estimating rate of change of receiver concentration (*dCr/dt*) in the calculation of the apparent permeability (Papp). Please use a minimum of three points to calculate the slope of the line for low, medium and high permeability drug substances.

DBE Comment 4:

For future submissions, please establish acceptable criteria for reporting percent recovery for permeability experiments in your Standard Operating Procedures (SOPs).

Firm's Response to Comment 3 and 4:

Barr acknowledges the above comments and recommendations.

4 REVIEWER'S COMMENT

The firm has satisfactorily responded to the deficiencies.

All BCS Committee members are in agreement that Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg should be classified as a BCS Class I drug, see Additional Attachments I section of the review for meeting minutes.

5 DEFICIENCY COMMENT

None

6 RECOMMENDATIONS

1. The Division of Bioequivalence finds the in vitro studies conducted by the firm, Barr Laboratories, Inc., to establish that its Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg is a Biopharmaceutics Classification System (BCS) Class I drug are acceptable.

2. The Division of Bioequivalence accepts the *in vitro* solubility study, Report No. MHT-826 conducted by the Barr Laboratories, Inc. on its Temozolomide Capsules, 250 mg, Lot No. 800104. Temozolomide is a highly soluble drug substance.

3. The Division of Bioequivalence accepts the *in vitro* permeability study, Report No. 7BARRP1R1GLPS34 conducted by the Barr Laboratories, Inc. Temozolomide is a highly permeable drug substance.

4. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing conducted by Barr Laboratories, Inc. on its Temozolomide Capsules, 5 mg (Batch No. 800090), 20 mg (Batch No. 800091), 100 mg (Batch No. 800102), 140 mg (Batch No. 800232), 180 mg (Batch No. 800235), and 250 mg (Batch No. 800104) demonstrated that this drug product is rapidly dissolving.

5. The dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL (for the 5 mg strength) and 900 mL (for the other strengths) of Dearated Water at 37ºC ± 0.5ºC using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specification:

   NLT (b) (4) (Q) of temozolomide dissolved in 30 minutes.

3. The Division of Bioequivalence deems the test product, Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, manufactured by Barr Laboratories, Inc. to be bioequivalent to the reference product, Temodar® (temozolomide) Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, manufactured by Schering-Plough Corporation, respectively.

6.1 Additional Attachments

BCS Committee Meeting Minutes

When: June 2009
Where: Ad Hoc

Meeting Participants:

Mehul Mehta (Co-Chair)	Director, DPE I, OCP
Lawrence Yu (Co-Chair)	Director for Science, OGD
Dakshina Chilukuri	Reviewer, DPE III, OCP
Dale Conner	Director, DBE I, OGD
Barbara Davit	Acting Director, DBE II, OGD
Sam Haidar	Reviewer, OGD
Ramana Uppoor	Team Leader, DPE I, OCP
Jayabharathi Vaidyanathan	Reviewer, DPE II, OCP
Donna Volpe	Researcher, LCP, OTR
Nam Chun	Executive Secretary, BCS Committee, OGD

Agenda:

BCS Classification of Temozolomide Capsules

Background:

In May 2009, the BCS Committee was asked to review information submitted in ANDA 78-879 in support of BCS classification of Temozolomide Capsules. Barr Laboratories, Inc. submitted a solubility study, an *in vitro* permeability study using cultured monolayers of Caco-2 cells, and an *in vitro* dissolution study to support a Biopharmaceutics Classification System (BCS) Class I waiver request for its product Temozolomide Capsules.

All committee members agreed Temozolomide is highly soluble and rapidly dissolving. However, six committee members stated that Temozolomide cannot be classified as highly permeable based on the information provided by the sponsor. The Committee requested that the reviewer further evaluates the published article on 'absolute bioavailability study' which indicates that the absolute bioavailability is > 90% and provide her comment on the scientific validity of the paper to support the adequacy of the *in vitro* experiments for permeability assessment.

On June 15, 2009, the DBE 1 reviewer submitted additional information on absolute bioavailability study on Temozolomide and requested that the BCS Committee re-evaluate ANDA 78-879 in support of BCS classification of Temozolomide Capsules.
See Attachment I and II for additional information.

Conclusion:

All committee members are in agreement that there is sufficient information to classify Temozolomide Capsules as a BCS Class I drug.

Vote:
Vote: Yes (9), No (0)

Drafted: Nam Chun 06/24/09

Comments :
D. Chilukuri : 06/18/09
D. Conner : 06/16/09
B. Davit: 05/04/09
S. Haidar: 06/15/09
M. Mehta: 06/18/09
J. Vaidyanathan: 06/15/09
D. Volpe: 06/15/09
R. Uppoor: 06/15/09
L. Yu: 06/22/09

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ATTACHMENT I

Absolute Bioavailability of Temozolomide

Summary of Cited Journal Articles in ANDA 78879 for Temozolomide

Newlands et al. [2], conducted two parts of a Phase I clinical trial with a total of 51 patients with advanced cancer (melanoma, renal, breast, colorectal, stomach, glioma and others) and a life expectancy of at least two months. In addition, the patients had normal liver function, urea and electrolytes, serum creatine, uric acid, glucose and coagulation screen.

The patients were treated with a single dose schedule of intravenous temozolomide ranging in doses from 50 mg/m^2 up to 200 mg/m^2. Temozolomide was administered as a one hour infusion after prior dilution in 500 ml of normal saline. Oral temozolomide was given in the form of hard gelatin capsules containing 20, 50, 100 and 250 mg to fasted individuals.

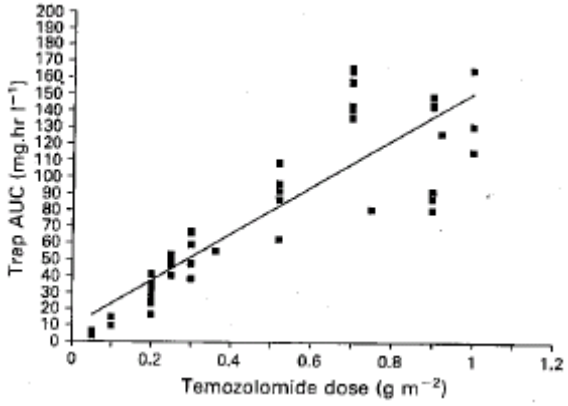
Of the 51 patients, 5 of the patients also received temozolomide both orally and intravenously on two separate occasions at least 4 weeks apart. The oral bioavailability over the dose range of 200 mg/m^2 up to 1200 mg/m^2 was good. The data from each patient is presented in Table 1 (i.v. dose: 200 mg/m^2 and oral dose: 200 mg/m^2).

Patient	i.v. AUC (mg h l^{-1})	Oral AUC (mg h l^{-1})	F^b
05	[redacted] (b) (4)		1.27
07			0.98
15			1.16
17			1.36
19			0.67
Mean			**1.09**

The Area Under the Curve (AUC) was calculated by the trapezoidal rule.
F^b – Bioavailability calculated without consideration of the small differences in apparent elimination half life.

After intravenous administration plasma temozolomide concentrations declined biexponentially and could be described by a two compartment model with a distribution half life of 1.8 hours. After oral dosing however, plasma concentrations in most instances have been fitted to a one compartment model. Temozolomide was rapidly absorbed, with maximum plasma concentrations being attained 0.7 hours post dosing. Over the concentration range studied, temozolomide pharmacokinetics were not dose dependent and the relationship between dose and the area under the plasma concentration vs. time curve was linear (r = 0.858) (see Figure 1). Clearance of temozolomide was estimated to be 11.8 l/h. Plasma temozolomide concentrations in some patients displayed a secondary absorptive phase as late as 4 hours post dosing which is likely to reflect entero-hepatic recycling.
Figure 1. Temozolomide dose versus Area Under the Plasma Concentration Curve

[2] Newlands, E. S., Blackledge, G. R. P., Slack, J. A., Rustin, G. J. S., Smith, D. B., Stuart, N. S. A., Quarterman, C. P., Hoffman, R., Stevens, M. F. G., Brampton, M. H., and A. C. Gibson. 1992. Phase I trial of temozolomide (CCRG 81045: M&B 39831: NSC 362856). *Br. J. Cancer*. 65: 287-91.



The data relating to the two patients receiving oral temozolomide on three separate occasions indicates that intra-subject variability in plasma concentrations is small.

The Phase I trial was targeted towards melanoma since at physiological pH, temozolomide spontaneously activates to 5-(3-methyltriazen-l-y)imidazole-4-carboxamide (MTIC) the putative active metabolite of dacarbazine, an existing anti-melanoma agent.

Additional Supportive Research Articles

In addition, Dhodapkar et al.[3] conducted a Phase I Clinical study with 36 patients with advanced cancer. Each patient received a total of 77 cycles of therapy with temozolomide. The trial was divided into two groups, those with or without prior exposure to nitrosourea (NU). The dose escalation was 50, 100, 150 and a decrease to 125 mg/m^2 for the prior NU group and 50, 100, 150, 200, 250, and a decrease to 225 mg/m^2 for the no prior NU group.

The pharmacokinetics were studied in 36 patients who received oral doses of 50-250 mg/m^2/day for 5 days. Due to the rapid absorption of temozolomide, plasma concentration time data were poorly fit by conventional compartmental analysis. Therefore, pharmacokinetic parameters were calculated using noncompartmental methods. Following a delay of approximately 10 minutes, temozolomide absorption was rapid, with peak plasma concentrations occurring 60 minutes (range, 20-240 min) after oral administration. The pharmacokinetic study showed that temozolomide was rapidly absorbed after a brief delay and rapidly cleared from plasma. It did not appear that temozolomide accumulated in the plasma, and plasma clearance was not altered by repeated administration. Dhodapkar et al. states that *Renal clearance of parent drug and metabolism to 3-methyl-2,3-dihydro-4-oxoimidazol [5,1-D]tetrazine-8-carboxylic acid (AM) were minor pathways for the elimination of temozolomide. The major route of elimination of temozolomide appeared to be chemical hydrolysis because high concentrations of 4-amino-5-imidazole-carboxamide (AIC), the final product of temozolomide hydrolysis, were detected in*

[3] Dhodapkar, M., Rubin, J., Reid, J. M., Burch, P. A., Pitot, H. C., Buckner, J. C., Ames, M. M., and V. J. Suman. Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer. 1997. *Clin. Cancer Res.* 3: 1093-1100.

plasma. These results are in agreement with the data reported by Newlands et al. and are consistent with bioequivalence of the machine filled capsules administered in our study with the hand-filled capsules administered in the trial of Newlands et al. Although Dhodapkar's study did not include a population of patients who received intravenous temozolomide, the authors postulated that the data are indicative of 100% oral bioavailability, based on similarity of the AUCs following an oral dose of 200 mg/m^2/day of temozolomide with those obtained in the trial of Newlands et al. following oral administration of a similar dose.

Mass Balance Study With Incomplete Recovery

Baker et al. [4] conducted a study to characterize the absorption, metabolism, and excretion of carbon 14-labeled temozolomide (^{14}C-TMZ) administered orally to 6 adult patients with advanced cancer. The patients received a single-oral dose of 200 mg. In the pharmacokinetic study, non-compartmental analysis was used. Temozolomide exhibited rapid absorption and high systemic availability after administration. Mean maximum temozolomide plasma concentrations were achieved at 1.2 h, which represented the majority (90%) of radioactivity in plasma. Blood and plasma radioactivity concentrations were detectable at the first sampling time point (0.33 h) and remained quantifiable at 168 h. Based on the pharmacokinetic study temozolomide was eliminated from plasma with concentrations not quantifiable after 8 h in 5 of the 6 patients. On average, < 1% of the ^{14}C-TMZ dose was recovered in the feces and 38% was recovered in the urine over the 360-h collection period. Baker et al, states that '*On the basis of the observed neglible fecal excretion of radioactivity (< 1% of dose), > 99% of the oral temozolomide dose was absorbed. These results are consistent with those reported in previous phase I studies, in which time to peak plasma concentrations were reported to be 1.0 h* (Dhodapkar, et al., 1997)*, and bioavailability after oral administration of an earlier capsule formulation to five patients was ~ 100%* (Newlands, et al., 1992).'

To explain the incomplete recovery of the radioactivity (i.e., <39% total), the above paper also states the following: *"…an assessment of the combined cumulative excretion of radioactivity in the urine (38%) and feces (<1%) out to 14 days after treatment indicates that recovery of radioactivity was incomplete. Because AIC* [the metabolite 4-amino-5-imidazole-carboxamide] *is an intermediate in purine biosynthesis, the incomplete recovery of radioactivity is likely due to the incorporation of AIC into the purine pool. Incorporation of AIC into the purine biosynthetic pathway has been demonstrated in a female volunteer administered ^{14}C-AIC. Analysis of urinary metabolites confirmed the presence of radiolabeled AIC, uric acid, xanthine, hypoxanthine, guanine, adenine, and 7-methylguanine. The unidentified polar metabolites measured in urine after administration of ^{14}C-TMZ* [carbon 14-labeled temozolomide] *could represent products formed by incorporation and metabolism of AIC in the purine and uric acid biosynthesis pathways. In addition, a small portion of the radiolabel may also have been eliminated as $^{14}CO_2$."*

It should be noted that the mass balance study in the above paper is the ***same*** mass balance study submitted in the NDA 21029 (Study #C95-006) and the basis for the statement in the current labeling of Temodar® capsules: *'**Excretion:** About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%).'*

Cited Articles for Temozolomide:

All articles are located in the following folder on the

[4] Baker, S. D., Wirth, M. W., Statkevich, P., Reidenberg, P., Alton, K., Sartorius, S. E., Dugan, M., Cutler, D., Batra, V., Grochow, L. B.., Donehower, R. C., and E. K. Rowinsky. Absorption, metabolism, and excretion of 14C-temozolomide following oral administration to patients with advanced cancer. 1999. *Clin. Cancer Res.* 5: 309-317

V:/ drive - V:\DIVISION\BIO\2009_BCS_Temozolomide

1. Newlands, et al., 1992

Newlands 1992.pdf

2. Dhodapkar, et al., 1997

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2009_BCS_Temozolor

3. Baker et al., 1999

V:\DIVISION\BIO\
2009_BCS_Temozolor

ATTACHMENT II

BCS Committee Meeting Minutes

When: May 2009

Where: Ad Hoc

Meeting Participants:

Mehul Mehta (Co-Chair)	Director, DPE I, OCP
Lawrence Yu (Co-Chair)	Director for Science, OGD
Dakshina Chilukuri	Reviewer, DPE III, OCP
Dale Conner	Director, DBE I, OGD
Barbara Davit	Acting Director, DBE II, OGD
Sam Haidar	Reviewer, OGD
Ramana Uppoor	Team Leader, DPE I, OCP
Jayabharathi Vaidyanathan	Reviewer, DPE II, OCP
Donna Volpe	Researcher, LCP, OTR
Nam Chun	Executive Secretary, BCS Committee, OGD

Agenda:

BCS Classification of Temozolomide Capsules

Background:

The DBE 1 requested that the BCS Committee review information submitted in ANDA 78-879 in support of BCS classification for Temozolomide Capsules. Barr Laboratories, Inc. submitted a solubility study, an *in vitro* permeability study using cultured monolayers of Caco-2 cells, and an *in vitro* dissolution study to support a Biopharmaceutics Classification System (BCS) Class I waiver request. The Committee was asked to evaluate the data for a final determination regarding BCS Class 1.
See Attachment I and II for additional information.

Conclusion:

1) Solubility: All committee members are in agreement that temozolomide is highly soluble.
2) Permeability: In addition, three committee members are in agreement that temozolomide is highly permeable. Six committee members stated that temozolomide cannot be classified as highly permeable based on the information provided by the sponsor. One dissenting member further recommended that the reviewer evaluates the published article on 'absolute bioavailability study' which indicates that the absolute bioavailability is > 90% and provide her comment on the scientific validity of the paper to support the adequacy of the *in vitro* experiments for permeability assessment. (**See Attachment III)**
3) Dissolution: All committee members are in agreement that temozolomide is rapidly dissolving.

Vote:
Vote: Yes (3) No (6)

Drafted: Nam Chun 05/12/09

Comments :
D. Chilukuri : 05/06/09
D. Conner : 05/12/09
B. Davit: 05/04/09
S. Haidar: 05/08/09
M. Mehta: 05/06/09
J. Vaidyanathan: 04/27/09
D. Volpe: 04/21/09
R. Uppoor: 05/04/09
L. Yu: 05/06/09

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BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-879

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you will conduct dissolution testing using the following FDA-recommended dissolution method and specification for your test product, Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg:

Medium:	Dearated Water
Volume:	500 mL for the 5 mg strength only 900 mL for the 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg strengths
Temperature:	37°C ± 0.5°C
USP Apparatus:	I (Basket)
Rotational Speed:	100 rpm

The test product should meet the following specification:

NLT (b) (4) Q) of Temozolomide Capsules dissolved in 30 minutes.

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

7 OUTCOME PAGE

ANDA: 78-879

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7603	2/6/2009	Other	Study Amendment	1	1
				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/

Deanah L Mitchell
7/6/2009 08:30:33 AM
BIOPHARMACEUTICS

April Braddy
7/6/2009 09:19:39 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
7/6/2009 01:51:20 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 078879

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Barr Laboratories, Inc.

223 Quaker Road · PO Box 2900 · Pomona, NY 10970-0519 · (845) 362-1100

March 19, 2007

Electronic Submission

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

In accordance with the regulations under section 505(j) of the Federal Food, Drug and Cosmetic Act, Barr Laboratories, Inc. ("Barr") is submitting an Abbreviated New Drug Application for **Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.**

Pursuant to 21 CFR Part 11.2(b) (2), this application is provided in Electronic Format on one CD-ROM of around 350 MB.

This electronic ANDA is located in the main folder labeled ANDA. Inside the main folder (ANDA) are four folders: *Module 1, Module 2, Module 3 and Module 5.* The documents and data files are organized as per the Guidance for Industry, *Submitting Marketing Applications According to the ICH-CTD Format – General Considerations.* Each item has an assigned subfolder where documents and data files that belong to the item are placed. For ease of navigation, a main table of contents, labeled **ANDA Table of Contents.pdf**, is provided with hyperlinks to each respective subfolder and its corresponding table of contents. This is located in the Module 1 folder.

A document containing a Quality Overall Summary (QOS) is located in **ANDA\Module 2\2.3 Quality Overall Summary.pdf**. The Module 2 folder also contains an MS Word version of the QOS.

This application contains the data for solubility, permeability, and dissolution described in the Guidance for Industry: "Waiver of In-Vivo Bioavailability and Bioequivalence Studies Based on Biopharmaceutics Classification System".

Based on the data in this application, Barr is proposing that temozolomide should be classified as a BCS Class I drug. The solubility, permeability, and dissolution data supporting our recommendation are located in Module 5.3.1.2.

We are providing the analytical methods information copy in electronic format. This information is provided in two separate files labeled **Method Validation** and they are located in the **ANDA\Module 3\3.2.R Regional Information.pdf** folder. *Barr commits to resolve any issues that may be identified in the enclosed method validation procedures during the review process or after approval.*

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 3/16/07 rev.19). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

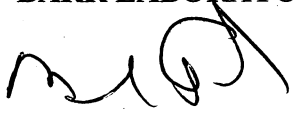
Included in this electronic submission and in accordance with the Generic Drug Enforcement Act of 1992 are Debarment Certification Statements from Barr and its outside contractors. These are located in the folder: **ANDA\Module 1.pdf**. In addition to an electronic copy of the FDA form 356h (**ANDA\Module 1\ 1.1.2 FDA-356h.pdf**), this form has been provided in the original paper format.

In accordance with 21 CFR Part 11.2(b) (2) and Docket 92S-0251 – Update Transmittal Memorandum 29, dated September 24, 2003, letters have been forwarded to the Baltimore and New York District Offices certifying that the electronic CMC section has been submitted to CDER and that the ORA District Office is able to access electronic CMC submissions through CDER's Electronic Document Room.

If you have any questions concerning this application, please contact Nicholas Tantillo at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.



Nicholas Tantillo
Senior Director,
Regulatory Affairs

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 : April 24, 2007

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 78-879 for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 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 78-879 for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 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 Marrch 19, 2007 for its Temozolomide 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
4/24/2007 11:53:58 AM
APPLICATIONS EXA

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 78-879 **FIRM NAME** **Barr Laboratories, Inc.**

DRUG NAME Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg.

DOSAGE FORM **Capsules**
SUBJ: Request for examination of: Request for BCS Waiver

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:

_____ Date: _____
Glendolynn S. Johnson
Reviewer

_____ Date: _____
Yih-Chain Huang
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☐	☒			N/A
Assay Methodology	☐	☒			N/A
Procedure SOP	☐	☒			N/A
Methods Validation	☐	☒			N/A
Study Results Ln/Lin	☐	☒			N/A
Adverse Events	☐	☒			N/A
IRB Approval	☐	☒			N/A
Dissolution Data	☒	☐			Module 5.3: Clinical Study Reports and Related Information
Pre-screening of Patients	☐	☒			N/A
Chromatograms	☐	☒			N/A
Consent Forms	☐	☒			N/A
Composition	☒	☐			Module 5: CTD summary tables: Dissolution Studies: table 5
Summary of Study	☐	☒			See comments
Individual Data & Graphs, Linear & Ln	☐	☒			N/A
PK/PD Data Disk Submitted)	☐	☒			N/A
Randomization Schedule	☐	☒			N/A
Protocol Deviations	☐	☒			N/A
Clinical Site	☐	☒			N/A
Analytical Site	☐	☒			N/A

Study Investigators	☐	☒			N/A
Medical Records	☐	☒			N/A
Clinical Raw Data	☐	☒			N/A
Test Article Inventory	☐	☒			N/A
BIO Batch Size	☐	☒			N/A.,
Assay of Active Content Drug	☒	☐			Module 3.2.P.5: Control of drug product
Content Uniformity	☒	☐			Module 5.3: Clinical Study Reports and Related Information page 120 of 142
Date of Manufacture	☒	☐			Module 5: CTD summary tables: Dissolution Studies (9/27/06)
Exp. Date of RLD	☒	☐			Module 5: CTD summary tables: Dissolution Studies (10/2008)
BioStudy Lot Numbers	☒	☐			Module 2.3.S.4 Control drug substance page 6 of 56
Statistics	☐	☒			N/A
Summary results provided by the firm indicate studies pass BE criteria	☐	☒			N/A
Waiver requests for other strengths / supporting data	☒	☐			Module 5 TOC: ANDA TOC: 1.12.15 (5 mg, 20 mg, 100 mg and 250 mg)

Additional Comments regarding the ANDA:

This submission is an electronic application. All of the requested information is located in the electronic document room (EDR). The application contains a BCS waiver request. The firm has submitted results of in vitro permeability study (Caco-2), solubility study, and dissolution testing (all in Module 5). The RLD product used by the firm for this application is Temodar® (temozolomide) capsules by Schering-Plough Corporation (NDA # 021-029, approved 8/11/1999).

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

/s/

Yih Chain Huang

5/14/2007 03:58:17 PM

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 1, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attn: Saundra Middleton, Project Manager

REFERENCE: ANDA # 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

New Correspondence

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Reference is also made to the Agency's telecommunications on May 29, 2007 between William Kwok of Barr and Saundra Middleton of FDA.

Ms. Middleton noticed that our claim for not including the indication, "I-450 for treatment of patients with newly diagnosed high grade gliomas concomitantly with radiotherapy and then as adjuvant treatment", in the Exclusivity Statement does not agree with the labeling listed on page 33 of Module 1.14.3.1: Annotated-Highlighted Comparison with Listed Drug. Barr's current labeling included the "I-450" indication. She asked Barr to make an appropriate correction to our labeling section and submit it as a new correspondence. She also requested Barr email her the corrected electronic files.

Barr is now submitting revised draft labeling to remove all references to the I-450 indication.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 5/31/07 rev. 19). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this labeling amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

Nicholas Tantillo
Senior Director, Regulatory Affairs

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 #: 78-879 **FIRM NAME**: BARR LABORATORIES, INC.

PIV: YES **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: TEMOZOLOMIDE
(BCS I CLASS PRODUCT)

DOSAGE FORM: CAPSULES, 5 MG, 20 MG, 100 MG, AND 250 MG

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☐ **BDI**	

Random Queue: 2
Chem Team Leader: Smela, Michael PM: Peter Chen Labeling Reviewer: Angela Payne

Letter Date: MARCH 19, 2007 **Received Date**: MARCH 20, 2007

Comments: EC - 4 YES **On Cards:** YES
Therapeutic Code: 5010100 CYTOXIC

Archival copy: PAPER (ECTD FORMAT) **Sections** I
Review copy: NA 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 Saundra T. Middleton	**Recommendation:**
Date 6/4/2007	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:

5/29/2007 – Barr (spoke with Bill Kwok) was asked to revised the side-by-side labeling to coincide with the exclusivity statement that indicated that I-450 (treatment of patients with newly diagnosed high grade gliomas concomitantly with radiotherapy and then as adjuvant treatment) will be omitted from the labeling.

Bill was also informed that before submitting a batch size less than (b) (4) **with scale up and exhibit size the sam) prior approval should be received from the chemistry division.**

6/4/2007 – Revised labeling submitted 6/1/2007 via e-mail. Electronic copy to follow.

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: MARCH 19, 2007	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
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) or Disclosure Statement (Form FDA 3455) NA	☐

1.3.5

1.3.5.1

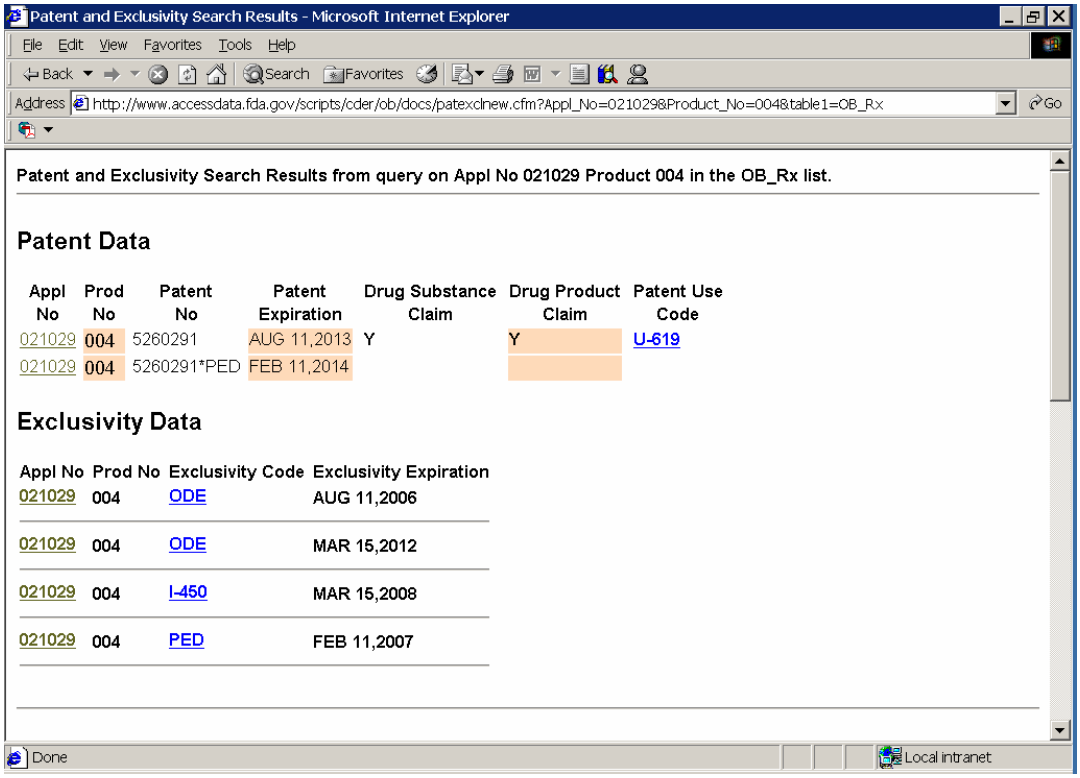
Patent Information

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) PIV 5'260'291
2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒
   No Relevant Patents ☐
3. Expiration of Patent(s): 2/11/2014
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES did not include ODE or I-450 in labeling



Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-619	TREATMENT OF MALIGNANT NEOPLASM

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
ODE	ORPHAN DRUG EXCLUSIVITY

Code	Definition
I-450	TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED HIGH GRADE GLIOMAS CONCOMITANTLY WITH RADIOTHERAPY AND THEN AS ADJUVANT TREATMENT

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 YES - # (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒
1.12.11	**Basis for Submission** NDA# : 21-029 Ref Listed Drug: TEMODAR Firm: SCHERING-PLOUGH CORPORATION 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 does not include I-450 (firm was asked to revised labeling to not include I-450) 2. Active ingredients YES 3. Inactive ingredients YES 4. Route of administration YES 5. Dosage Form YES 6. Strength YES	☐
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Electronic, YES BCS (SEE BELOW)	☒

3. Comparison of the Generic Drug versus Reference Listed Drug

Manufacturer:	Schering-Plough Corporation	**Barr Laboratories, Inc.**
Drug Name:	Temodar® (Temozolomide) Capsules	Temozolomide Capsules
1. Conditions for Use	Temodar® capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. Temodar® capsules also are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.	Temozolomide capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES – per exclusivity certification reference to I-450 should not be in the labeling: I-450 TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED HIGH GRADE GLIOMAS CONCOMITANTLY WITH RADIOTHERAPY AND THEN AS ADJUVANT TREATMENT **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.) **INDICATIONS AND USAGE** (b) (4) ~~TEMODAR~~Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. **REVISED LABELING SUBMITTED VIA E-MAIL 6/1/2007:** **INDICATIONS AND USAGE** (b) (4) ~~TEMODAR~~Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.	☐
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 YES **1.14.3.3** 1 RLD label and 1 RLD container label YES 5 AND 20 COUNT EACH	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: YES PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _____ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) YES** **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 YES** **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) NO** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☐

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature YES** **3.2.S.1.2** **Structure YES** **3.2.S.1.3** **General Properties YES**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES # (b) (4) 4. CFN or FEI numbers YES	☒
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) YES **3.2.S.4.2** **Analytical Procedures** YES **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **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 YES 2) Inactive ingredients are appropriate per IIG YES – SEE BELOW	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
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) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers SOME **3.2.P.3.2** **Batch Formula** Batch Formulation YES **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES – SEE BELOW 3. If sterile product: Aseptic fill / Terminal sterilization YES 4. Reprocessing Statement YES **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation - NA** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** YES Source of inactive ingredients identified YES **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **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 YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** YES **3.2.P.5.2** **Analytical Procedures** YES **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **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) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 24 MONTHS **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES	☒

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)** YES **3.2.R.2.S** **Comparability Protocols** YES **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

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 YES – SEE BELOW **3.2.R.1.P.2** **Information on Components** NO **3.2.R.2.P** **Comparability Protocols NO** **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)	☒

(b) (4)

[redacted]

Following this page, 1 page withheld in full (b)(4)

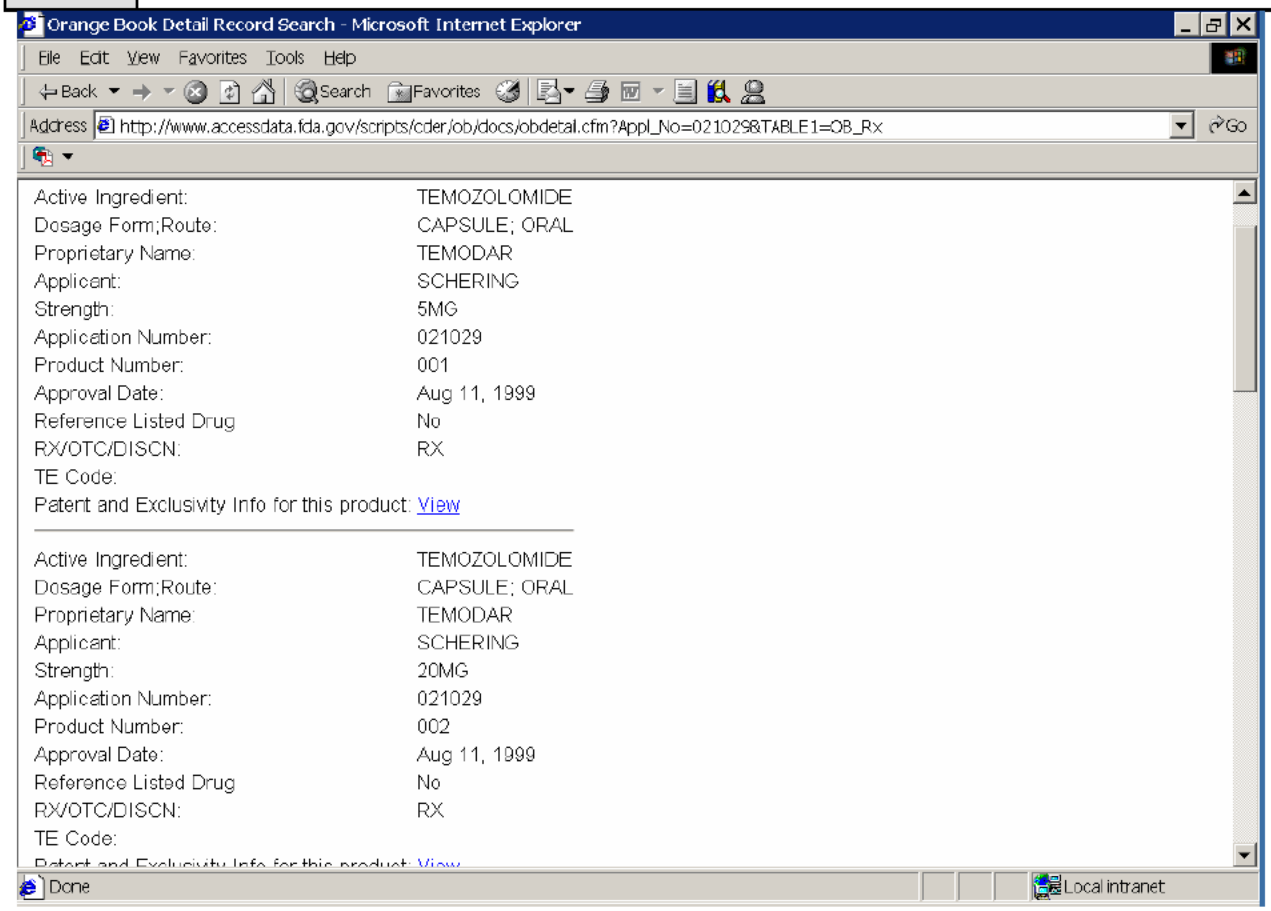
MODULE 5
CLINICAL STUDY REPORTS

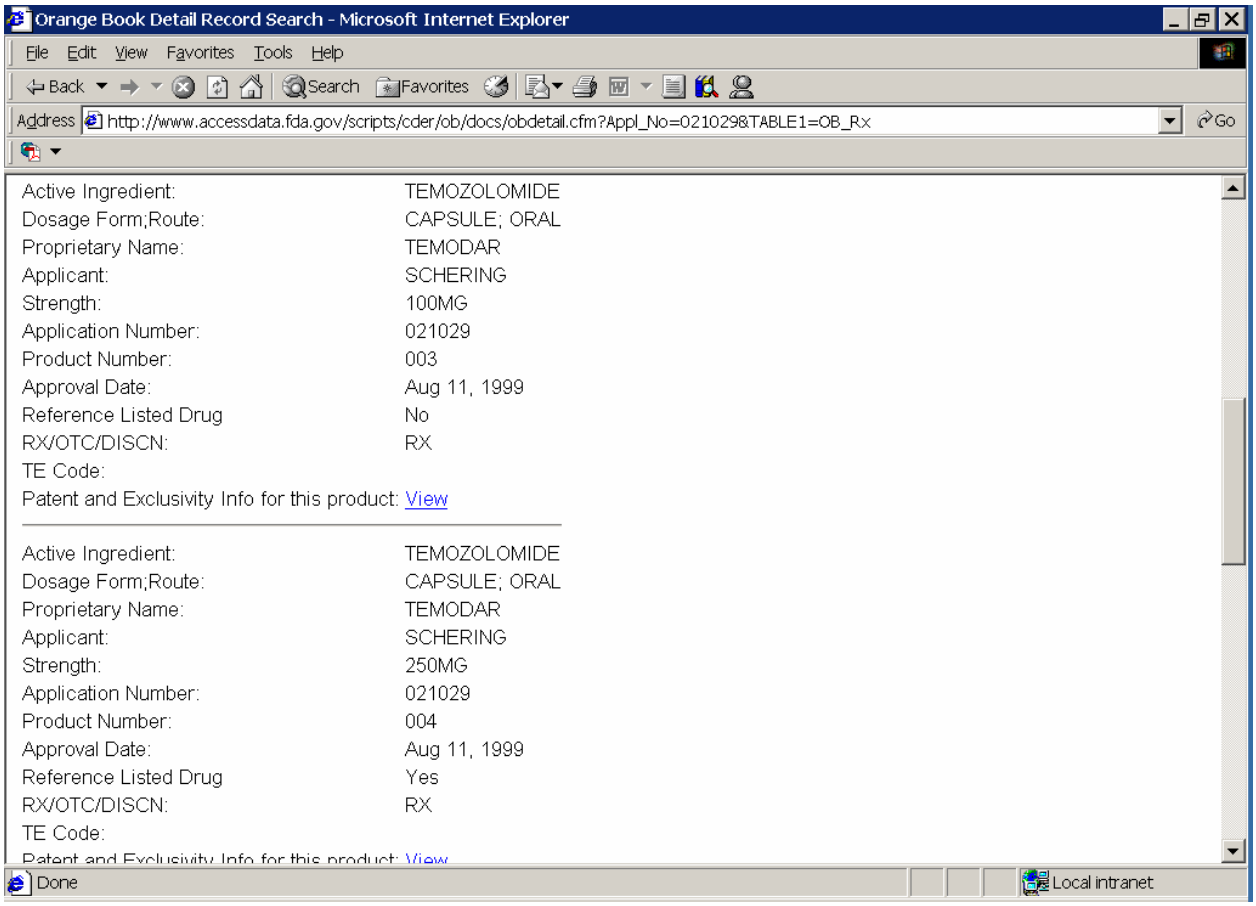
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
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: IN-VIVO PK STUDY(IES)** (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 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports – BCS CLASS I WAIVER REQUEST ACCEPTED SEE DBE CHECKLIST IN DFS** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies YES Table 5. Formulation Data YES **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **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) NA 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: NO	☐
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** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 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% or 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, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 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	☐

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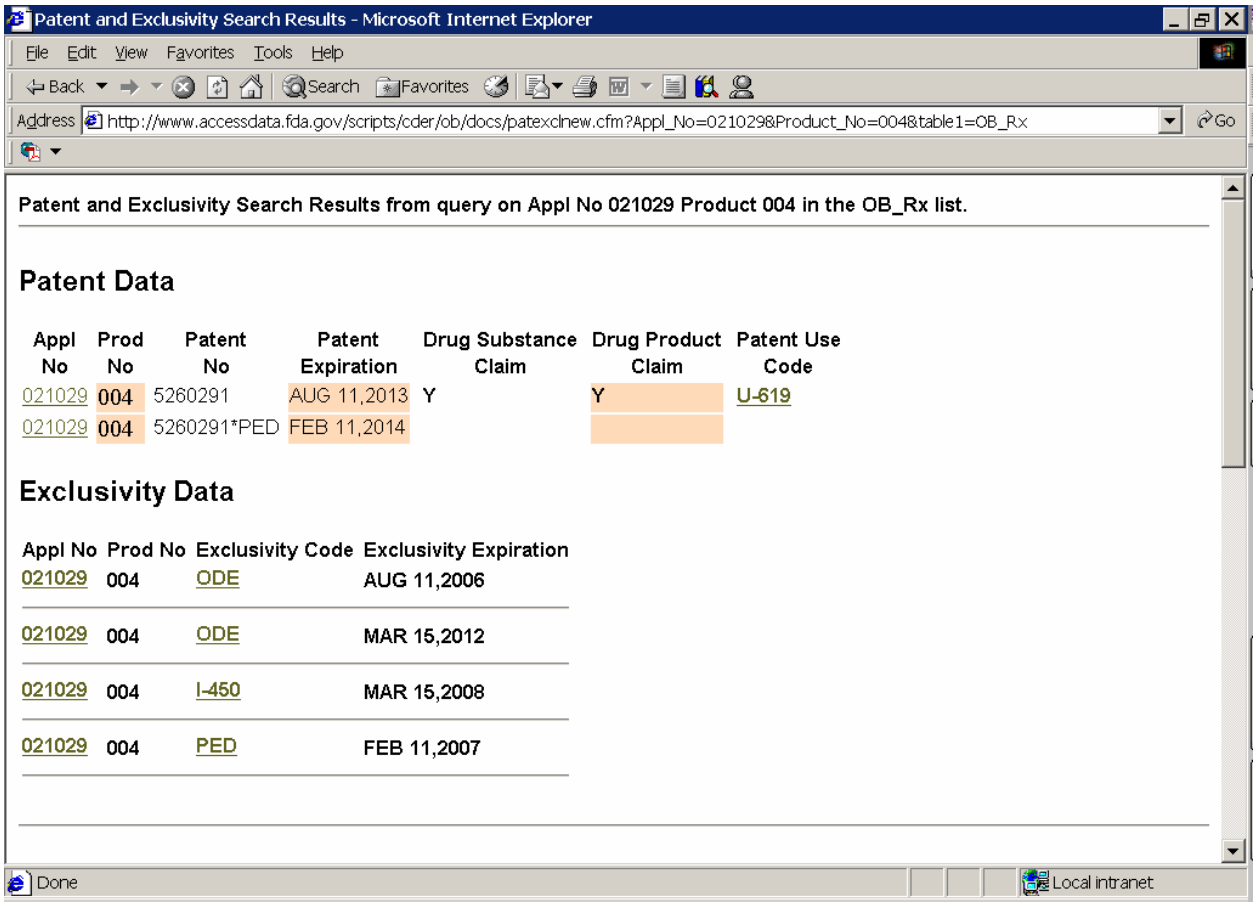
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021029&TABLE1=OB_Rx
Go
Active Ingredient: TEMOZOLOMIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: TEMODAR
Applicant: SCHERING
Strength: 100MG
Application Number: 021029
Product Number: 003
Approval Date: Aug 11, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: TEMOZOLOMIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: TEMODAR
Applicant: SCHERING
Strength: 250MG
Application Number: 021029
Product Number: 004
Approval Date: Aug 11, 1999
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Done
Local intranet



Patent and Exclusivity Search Results from query on Appl No 021029 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021029	004	5260291	AUG 11,2013	Y	Y	U-619
021029	004	5260291*PED	FEB 11,2014			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021029	004	ODE	AUG 11,2006
021029	004	ODE	MAR 15,2012
021029	004	I-450	MAR 15,2008
021029	004	PED	FEB 11,2007

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

/s/

Iain Margand
6/7/2007 01:39:15 PM
Signing for Martin Shimer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-879

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 made to telephone conversation dated May 29, 2007 and your e-mail dated June 1, 2007.

NAME OF DRUG: Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

DATE OF APPLICATION: March 19, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 20, 2007

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 court order or judgement 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 (301) 827-0503.

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:

Esther Chuh
Project Manager
(301) 827-5773

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/

Iain Margand
6/7/2007 01:40:07 PM
Signing for Wm. Peter Rickman

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 28, 2007

Off ice of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Reference is also made to the notice requirements outlined in the FDA's June 7, 2007 letter acknowledging receipt of the original ANDA.

In accordance with our Patent Certification Statement submitted in Module 1, Section 1.3.5.2 of the above referenced original application and 21 CFR §314.95(a), the notice with respect to U.S. Patent No. 5,260,291 was sent by certified mail on June 8, 2007, return receipt requested to the owner of the patent which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(b), Barr is hereby submitting a Patent Amendment to certify that notice was provided to Schering-Plough Corporation (owner of U.S. Patent No. 5,260,291 and NDA holder) by Sterne, Kessler, Goldstein and Fox P.L.L.C on behalf of Barr.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites the appropriate section of the Act. In the notice letter, Barr alleges that in its opinion U.S. Patent No. 5,260,291 is invalid, unenforceable or will not be infringed by the manufacture, use, or sale of Barr's Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

In accordance with 21 CFR §314.95(e), enclosed please find a copy of the signed return receipt from Schering-Plough Corporation for the notice, which was delivered on June 12, 2007.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 6/27/07 rev.16). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

ROPES &GRAY

FISH & NEAVE IP GROUP

ROPES & GRAY LLP
1211 AVENUE OF THE AMERICAS NEW YORK, NY 10036-8704 212-596-9000 F 212-596-9090
BOSTON NEW YORK PALO ALTO SAN FRANCISCO WASHINGTON, DC www.ropesgray.com

PM Notice that Suit was filed for '291 CA 07-CV-00457 S.M. 11/26/07

Denise L. Loring
212-596-9069
Denise.Loring@ropesgray.com

July 26, 2007

ORIG AMENDMENT
MC

Notification of Filing of Action
For Patent Infringement

VIA FACSIMILE AND FEDEX

Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

RECEIVED
JUL 27 2007
OGD

Re: ANDA No. 78-879
Temozolomide Capsules,
5 mg, 20 mg, 100 mg and 250 mg

Dear Sir or Madam:

Pursuant to Section 314.107(f)(2) of the regulations, this is to notify you that an action for patent infringement relevant to the above referenced ANDA application was filed by Cancer Research Technology Limited, the patent owner, and Schering Corporation, the exclusive licensee and the approved NDA holder, on July 20, 2007. The above-referenced application was filed by Barr Laboratories, Inc.

On or about June 13, 2007, Schering-Plough Corporation, the parent company of Schering Corporation, which is the exclusive licensee of U.S. Patent No. 5,260,291 ("the '291 patent"), received notice pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act ("the Act") dated June 8, 2007 from Barr Laboratories, Inc., applicant for the above referenced ANDA. The '291 patent is listed in the Orange Book for TEMODAR® (temozolomide) Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg.

On July 20, 2007, Cancer Research Technology Limited and Schering Corporation filed an action against Barr Laboratories, Inc. and its parent company, Barr Pharmaceuticals, Inc., for infringement of the '291 patent in the United States District Court for the District of Delaware, Civil Action No. 07-cv-00457.

Under Section 505(j)(5)(B)(iii) of the Act and Section 314.107(b)(3) of the regulations, based on the filing of this action, the above referenced ANDA application may not be made effective until December 13, 2009 (*i.e.*, 30 months from June 13, 2007), unless the court extends or reduces this period.

Respectfully submitted,

Denise L. Loring

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 26, 2007

Off ice of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg and the notice requirements outlined in the FDA's June 7, 2007 letter acknowledging receipt of the original ANDA.

Reference is also made to the June 28, 2007 Patent Amendment in which Barr certified that the required notice letter was sent on June 8, 2007, to the owner of U.S. Patent No. 5,260,291 which is the subject of the certification, and to the holder of the approved application under Section 505(b) of the Act by certified mail. The notice letter was delivered on June 12, 2007.

Litigation with respect to U.S. Patent No. 5,260,291 has occurred within the 45-day period. On July 20, 2007, a formal complaint was filed by Schering Corporation and Cancer Research Technology Limited, against Barr, in the United States District Court of Delaware: Schering Corporation and Cancer Research Technology Limited v. Barr Laboratories, Inc., and Barr Pharmaceuticals, Inc. Civil Action No. 07cv457. A copy of the complaint letter is attached.

We will submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between Barr and the holder of the patent, or any other relevant information when it becomes available.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 7/25/07 rev.23). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 23, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attn: Keri Suh, Project Manager

REFERENCE: ANDA # 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

Telephone Amendment

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Reference is also made to the Agency's telecommunications on August 23, 2007 between William Kwok of Barr and Keri Suh of FDA.

Ms. Suh noticed the following discrepancies in our CTD summary tables:

- The dissolution data listed in CTD Summary Tables 1 and 3 does not matches the data listed on pages 102 and 108 of Module 5.3.1.3 – In Vitro-In Vivo Comparative Study Reports, respectively.
- The dissolution volume listed in CTD Summary Table 4 does not matches the dissolution volume listed on page 125 of Module 5.3.1.3 – In Vitro-In Vivo Comparative Study Reports

She asked Barr to make the appropriate correction to the CTD Summary tables and submit it as a telephone amendment.

Barr is now submitting revised CTD Summary tables (Tables 1, 3 and 4) in this Telephone Amendment.

Barr Laboratories, Inc.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 8/22/07 rev. 9). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this labeling amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

Nicholas Tantillo
Senior Director, Regulatory Affairs

ROPES & GRAY LLP
1211 AVENUE OF THE AMERICAS NEW YORK, NY 10036-8704 212-596-9000 F 212-596-9090
BOSTON NEW YORK PALO ALTO SAN FRANCISCO WASHINGTON, DC www.ropesgray.com

PA Suit Filed for '291 S. Wiseman 9/18/07

Denise L. Loring
212-596-9069
Denise.Loring@ropesgray.com

September 7, 2007

Notification of Filing of Action For Patent Infringement

ORIG AMENDMENT
N/A P

VIA FACSIMILE AND FEDEX

Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

Re: ANDA No. 78-879
Temozolomide Capsules,
5 mg, 20 mg, 100 mg and 250 mg

Dear Sir or Madam:

This is further to my July 26, 2007 letter pursuant to Section 314.107(f)(2) of the regulations, notifying you that on July 20, 2007, Cancer Research Technology Limited and Schering Corporation filed an action for infringement of U.S. Patent No. 5,260,291 ("the '291 patent") against Barr Laboratories, Inc., the holder of the above-referenced ANDA application. The '291 patent is listed in the Orange Book for TEMODAR® (temozolomide) Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg. A copy of my July 26 letter is attached at Tab A.

My July 26 letter informed you of Barr's notice to Schering Corporation pursuant Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act ("the Act"). Schering Corporation is the owner of the TEMODAR® NDA. Based on Schering Corporation's receipt of that notice on June 13, 2007, we informed you that Barr's ANDA may not be made effective until December 13, 2009, 30 months from June 13, 2007, unless the court extends or reduces this period.

In a letter dated, July 26, 2007, Barr Laboratories forwarded to Cancer Research Technology Limited, the owner of the '291 patent, a copy of its notice letter to Schering Corporation. Cancer Research Technologies Limited received that letter on July 27, 2007.

Accordingly, under Section 505(j)(5)(B)(iii) of the Act and Section 314.107(b)(3) of the regulations, the above referenced ANDA application may not be made effective until January 27, 2010 (*i.e.*, 30 months from July 27, 2007, the date by which both the patent holder Cancer Research Technology Limited and the NDA holder Schering Corporation received notice of Barr Laboratories' ANDA), unless the court extends or reduces this period.

Respectfully submitted,

Denise L. Loring

DLL:ac
Enclosure

BIOEQUIVALENCY AMENDMENT

ANDA 78-879

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Barr Laboratories, Inc. TEL: 201-930-3650

ATTN: Nicholas Tantillo FAX: 201-930-3318

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 19, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 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 **one** 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:

BIOEQUIVALENCE DEFICIENCY

ANDA: 078879

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 250 mg

The Division of Bioequivalence has completed its review of the non-BCS waiver related dissolution testing portion of the submission acknowledged on the cover sheet. The review of the other studies will be conducted later. The following deficiencies have been identified:

1. Please acknowledge the following dissolution method and specification:

Apparatus:	I (basket)
Speed:	100 rpm
Medium:	Deaerated Water
Volume:	500mL for 5mg strength, 900mL for other strengths
Temperature:	37°±0.5°C

Specification: NLT (b) (4) *(Q) in 30 minutes.*

2. If in your *in vitro-in vivo* comparative studies with deaerated water you used dissolution volumes of 500mL for the 5mg strength and 900mL for all other strengths, then please modify the information on p.98 of Module 5.3 accordingly.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
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/

Barbara Davit
9/13/2007 11:17:08 AM
Signing for Dale P Conner

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date Requested: 9/11/2007

TO: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence (HFD-48)
Division of Scientific Investigations
MPN 1

FROM: Dale P. Conner, Pharm. D._____
Director, Division of Bioequivalence, HFD-650

SUBJECT: Biopharmaceutics Compliance Program 7348.001

REQUEST FOR INSPECTION:

Electronic Submission: Yes
Priority: C
Due Date: 12/11/2007

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	078879
Drug Product Name	Temozolomide Capsules
Strength (s)	5mg, 20mg, 100mg, and 250mg
Applicant Name	Barr Laboratories, Inc.
Address	223 Quaker Road P.O. Box 2900 Pomona, NY 10970
Applicant's Point of Contact	Nicholas Tantillo
Contact's Phone Number	201-930-3650
Contact's Fax Number	201-930-3318
Submission Date(s)	Original: March 19, 2007 Telephone Amendment: August 23, 2007 Other amendments were filed that do not pertain to this review.
First Generic	Yes
Reviewer	Utpal M. Munshi, Ph.D.
Study Number (s)	7BARRP1R1GLPS34
Study Type (s)	*In vitro* permeability study
Strength(s)	N/A
Permeability Study Lab	(b) (4)
Permeability Study Lab Address	
Analytical Site	
Analytical Address	

Reason for Inspection: Routine Inspection
Comments:

Permeability in vitro study: cell culture and analytical
Solubility, Instability and Dissolution: analytical

Bio Study Status: Under Review
Project Manager: Keri Suh

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

/s/

Barbara Davit
9/13/2007 05:06:18 PM
Signing for Dale P Conner

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 5, 2007

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Bioequivalence Amendment

REFERENCE: ANDA # 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Reference is also made to the Agency's September 13, 2007 letter in which the Agency had the following comments:

Comment 1:

Please acknowledge the following dissolution method and specification:

Apparatus: I (basket)
Speed: 100 rpm
Medium: Deaerated water
Volume: 500 mL for 5 mg strength, 900 mL for other strengths
Temperature: 37° +/- 0.5°C

Specification: NLT (b) (4) (Q) in 30 minutes

Response 1:

Barr acknowledges the Agency's proposed test parameters and specification for dissolution, and updated the finished product test method to incorporate the proposed test parameters and specification. Please see Module 5 for a copy of the test method, MTH- 826.

Comment 2:

If in your in vitro- in vivo comparative studies with deaerated water you used dissolution volumes of 500 mL for the 5 mg strength and 900 mL for all other strengths, then please modify the information on p.98 of Module 5.3 accordingly.

Response 2:

Barr modified the dissolution volume information in the referenced page in Module 5.3, please see the revised information in this amendment (Module 5.3-Clinical Study Reports and Related Information).

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 10/4/07 rev.20). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

If you have any questions concerning this amendment, please contact me at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 18, 2007

Off ice of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT AMENDMENT

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg and the notice requirements outlined in the FDA's June 7, 2007 letter acknowledging receipt of the original ANDA.

In accordance with our Patent Certification Statement submitted in Module 1, Section 1.3.5.2 of the above referenced original application and 21 CFR §314.95(a), the notice with respect to U.S. Patent No. 5,260,291 was sent by certified mail on July 26, 2007, return receipt requested to the owner of the patent which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(b), Barr is hereby submitting a Patent Amendment to certify that notices were provided to Cancer Research Technology Limited and Cancer Research Technology Inc. (owners of U.S. Patent No. 5,260,291) by Sterne, Kessler, Goldstein and Fox P.L.L.C on behalf of Barr.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites the appropriate section of the Act. In the notice letter, Barr alleges that in its opinion U.S. Patent No. 5,260,291 is invalid, unenforceable or will not be infringed by the manufacture, use, or sale of Barr's Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

In accordance with 21 CFR §314.95(e), enclosed please find a copy of the signed return receipt from Cancer Research Technology Limited and Cancer Research Technology Inc. for the notice, which was delivered on July 31, 2007.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 10/17/07 rev. 18). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Telephone Fax

ANDA 78-879

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Barr Laboratories

TEL: 201-930-3650

ATTN: Nicholas Tantillo

FAX: 201-930-3318

FROM: Mrs. Angela Payne

Dear Sir:

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 Temozolomide Capsule.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: 78-879 Date of Submission: June 1, 2007 and Mar 19, 2007

Applicant's Name: Barr laboratories

Established Name: Temozolomide Capsule 5 mg, 20 mg, 100 mg, and 250 mg

---

Labeling Deficiencies: June 1, 2007 submission revised May 2007.

1. CONTAINER - 5s and 20s unit- of -use bottles

   Decrease the prominence of the total content. We recommend decreasing the font size and do not highlight. It appears to be in close proximity to the product strength and the 20 package size could be mistaken as the strength. Please ensure the caps for the uit-of-use bottles are child resistant. Ensure each strength is differentiated by the color codes used for the innovator product that corresponds to the color band around the capsules.

2. PROFESSIONAL INSERT- You stated in your patent and exclusivity statement that you do not plan to include the ODE and I-450 indications in your labeling. Please ensure text regarding these indications are carved out of your labeling. We specifically refer you to the following sections: WARNINGS, second paragraph; PRECAUTIONS, Laboratories Tests, first sentence and; ADVERSE REACTIONS, first section and table 1 prior to Refractory Anaplastic Astrocytoma subsection.

3. PATIENT INSERT - Remove the following text regarding I-450 seen under How should I take Temozolomide, third paragraph "for 42 days (up to 49) with radiotherapy. Another". In addition, use the full established name in the running text.

4. PHARMACIST INFORMATION SHEET- Delete text regarding the protected exclusivities for ODE (Newly Diagnosed High grade Gliomas concomitantly with Radiotherapy and then as maintenance therapy and the associated I-450 exclusivities "Newly diagnosed Concomitant Phase treatment Schedule" followed by the Maintenance Phase treatment Schedule subsections found in the pharmacist information sheet.

Revise your labels 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 and the latest approved labeling for the reference listed drug (or your last 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
10/19/2007 10:09:59 AM
for Wm Peter Rickman

MINOR AMENDMENT

ANDA 78-879

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Barr Laboratories, Inc. TEL: 201-930-3650

ATTN: Nicholas Tantillo FAX: 201-930-3318

FROM: Rosalyn Adigun PROJECT MANAGER: (301)-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 19, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (3 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. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

See Chemistry comments provided.

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

Chemistry Comments to be provided to the Applicant

ANDA: 78-879 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules 5 mg, 20 mg, 100 mg, and 250 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. DMF (b) (4) is inadequate. Please ensure a response from the DMF holder.

2. (b) (4)

3. Please include (b) (4).

4. Please modif (b) (4)

5. Please develop (b) (4)
.

6. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.

2. Information related to labeling and bioequivalency is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

Sincerely yours,

{See appended signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry 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/

James Fan
11/7/2007 01:04:43 PM
James M. Fan for Rashmikant Patel

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

December 20, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

LABELING AMENDMENT – ELECTRONIC SUBMISSION

REFERENCE: ANDA # 78-879
Temozolomide Capsules 5 mg, 20 mg, 100 mg, and 250 mg

Reference is made to our pending Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg.

Reference is also made to the Agency's October 19, 2007 Facsimile from Mrs. Angela Payne, in which labeling comments were provided.

Concerning the container labels, the recommendations to decrease font size, move the total content statements and incorporate the colors used by the innovator to differentiate each strength have been made.

Barr revised the color of the container label to match the color imprinted on the capsules. In addition, Barr will use a child resistant cap (CRC) for the packaging of these products.

Concerning the comments regarding the Professional Insert, Patient Insert, and Pharmacist Information Sheet, the reference and text related to the I-450 and ODE have been removed.

Attached please find the electronic Final Printed Labeling Submission for each of the following, with the changes requested in the fax transmission:

• Container Label	5 mg, 5 Capsules	10001522	Revision R12-07 (v. 1)
• Container Label	5 mg, 20 Capsules	10001521	Revision R12-07 (v. 1)
• Container Label	20 mg, 5 Capsules	10001523	Revision R12-07 (v. 1)
• Container Label	20 mg, 20 Capsules	10001518	Revision R12-07 (v. 1)

- Container Label 100 mg, 5 Capsules 10001517 Revision R12-07 (v. 1)
- Container Label 100 mg, 20 Capsules 10001516 Revision R12-07 (v. 1)
- Container Label 250 mg, 5 Capsules 10001520 Revision R12-07 (v. 1)
- Container Label 250 mg, 20 Capsules 10001519 Revision R12-07 (v. 1)
- Package Brochure 11001280 Revision OCTOBER 2007

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 12/19/2007 rev. 7). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this labeling amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

for Nicholas Tantillo
Senior Director, Regulatory Affairs

Telephone Fax

ANDA 78-879

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Barr Laboratories

TEL: 201-930-3650

ATTN: Nicholas Tantillo

FAX: 201-930-3318

FROM: Mrs. Angela Payne

Dear Sir:

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 Temozolomide Capsule.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-879 Date of Submission: 20 DEC 2007

Applicant's Name: Barr laboratories

Established Name: Temozolomide Capsule 5 mg, 20 mg, 100 mg, and 250 mg

---

Labeling Deficiencies:

1. CONTAINER - 5s and 20s unit- of -use bottles

   a. Add to the dispensing statement - "or retain in original bottle." In addition, place "Caution: Cytotoxic agent- Special Handling" in red print on the pain panel rather than the side panel for prominence.

   b. We recommend providing a carton to protect the consumer from the possibility of glass breakage that may result in damage to the capsules and direct patient/consumer contact with the drug content.

2. PROFESSIONAL INSERT-

   a. You stated in your patent and exclusivity statement that you do not plan to include the ODE and I-450 indications in your labeling. Please ensure that the text regarding these indications is carved out of your labeling. We specifically refer you to the following section: PRECAUTIONS, Geriatrics. 3rd paragraph.

   b. Prior to the Description section place a statement informing the pharmacist that a patient information and pharmacist's information sheets are attached.

3. PATIENT INSERT -

   a. Please explain the accessibility of the patient information sheet to the patient. Will the patient information sheet become a separate sheet attached to the bottle, inside the bottle, on a pad, etc? How will the pharmacist obtain the information sheet to give to the patient?

   b. Add "Pharmacist: Tear at perforations and give to patients."

4. PHARMACIST INFORMATION SHEET- Satisfactory.

Revise your labels 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 and the latest approved labeling for the reference listed drug (or your last 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
1/28/2008 12:42:30 PM
for Wm Peter Rickman

Barr Laboratories, Inc.

223 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 12, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

LABELING AMENDMENT – ELECTRONIC SUBMISSION

REFERENCE: ANDA # 78-879
Temozolomide Capsules 5 mg, 20 mg, 100 mg, and 250 mg

Reference is made to our pending Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg.

Reference is also made to the Agency's January 29, 2008 Facsimile in which labeling comments were provided.

Barr revised the container labels, package brochure and patient information sheet as recommended. Also, as recommended by the Agency, Barr will be implementing a folding carton to protect the consumer from the possibility of glass breakage that may result in damage to the capsules and direct patient/consumer contact with the drug content. The Pharmacist Information Sheet was found satisfactory.

Concerning your comment on the accessibility of the patient information sheet to the patient, there is a patient information sheet attached to each package insert with each container. The pharmacist will be able to detach the patient information sheet and provide it with each bottle or each prescription or leave it intact and provide the completed labeling to the patient at the time of dispensing.

Attached please find the electronic Final Printed Labeling Submission for each of the following:

Container Labels

5 mg, 5 Capsules	10001522	Revision R2-08 (v. 1)
5 mg, 20 Capsules	10001521	Revision R2-08 (v. 1)
20 mg, 5 Capsules	10001523	Revision R2-08 (v. 1)
20 mg, 20 Capsules	10001518	Revision R2-08 (v. 1)

Container Labels (continued)

100 mg, 5 Capsules	10001517	Revision R2-08 (v. 1)
100 mg, 20 Capsules	10001516	Revision R2-08 (v. 1)
250 mg, 5 Capsules	10001520	Revision R2-08 (v. 1)
250 mg, 20 Capsules	10001519	Revision R2-08 (v. 1)

Carton Labels

5 mg, 5 Capsules	15001207	Revision R2-08 (v. 1)
5 mg, 20 Capsules	15001206	Revision R2-08 (v. 1)
20 mg, 5 Capsules	15001203	Revision R2-08 (v. 1)
20 mg, 20 Capsules	15001202	Revision R2-08 (v. 1)
100 mg, 5 Capsules	15001201	Revision R2-08 (v. 1)
100 mg, 20 Capsules	15001200	Revision R2-08 (v. 1)
250 mg, 5 Capsules	15001205	Revision R2-08 (v. 1)
250 mg, 20 Capsules	15001204	Revision R2-08 (v. 1)

Package Brochure

11001280 Revision FRBRUARY 2008

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 2/11/2008 rev. 4). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this labeling amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

March 17, 2008

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

MINOR AMENDMENT

REFERENCE: **ANDA 78-879**
Temozolomide Capsules, 5mg, 20 mg, 100 mg, and 250mg

Reference is made to Barr Laboratories, Inc.'s ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250mg.

Reference is also made to the Agency's November 7, 2007 letter in which the Agency had the following comments. The Agency indicated that Barr's response would be considered a MINOR AMENDMENT.

Comment 1:

DMF (b) (4) **is inadequate. Please ensure a response from the DMF holder.**

Response 1:

(b) (4)

[redacted]

Following this page, 5 pages withheld in full (b)(4)

B: In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Comment 1:

Please provide all long-term stability data.

Response 1:

Barr is providing up to 12 months of stability data under long term conditions for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg in Module 3.2.P.8.

Comment 2:

Information related to labeling and bioequivalency is under review. After the reviews are completed, any deficiencies found will be communicated to you under separate covers.

Response 2:

Barr acknowledges that the bioequivalence and labeling sections of our application are under review and that deficiencies, if any, will be communicated to us under separate cover.

Comment 3:

The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

Response 3:

Barr acknowledges that all the firms listed in our ANDA application relative to manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is virus-free and was checked by using Symantec's AntiVirus Corporate Edition Software (Version 3/16/08 rev. 2). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

In accordance with 21 CFR Part 11.2(b) (2) and Docket 92S-0251 – Update Transmittal Memorandum 29, dated September 24, 2003, letters have been forwarded to the Baltimore and Ohio District Offices certifying that the electronic CMC section has been submitted to CDER and that the ORA District Office is able to access electronic CMC submissions through CDER's Electronic Document Room.

If you have any questions concerning this submission, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

March 21, 2008

Electronic Submission

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Amendment for addition of 140 mg and 180 mg strengths

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg

Reference is made to Barr Laboratories Inc.'s ('Barr') Abbreviated New Drug Application dated March 19, 2007, submitted in accordance with the regulations under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Barr is amending the above referenced application to seek approval for two (2) additional strengths of the product, Temozolomide Capsules, 140 mg and 180 mg. The 140 and 180 mg capsules are proportionally similar to Barr's Temozolomide Capsules, 250 mg and are produced by the same manufacturing process. The active ingredient and excipients used for the 140 and 180 mg capsules are from the same sources that were used in the manufacturing of Barr's Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Pursuant to 21 CFR Part 11.2(b) (2), this application is provided in Electronic Format on one CD-ROM of around 200 MB.

This electronic ANDA is located in the main folder labeled ANDA. Inside the main folder (ANDA) are four folders: *Module 1, Module 2, Module 3 and Module 5.* The documents and data files are organized as per the Guidance for Industry, *Submitting Marketing Applications According to the ICH-CTD Format – General Considerations.* Each item has an assigned subfolder where documents and data files that belong to the item are placed. For ease of navigation, a main table of contents, labeled **ANDA Table of Contents.pdf**, is provided with hyperlinks to each respective subfolder and its corresponding table of contents. This is located in the Module 1 folder.

Please refer to the document containing a Quality Overall Summary (QOS) submitted in the original ANDA 78-879 located in Module 2/2.3 Quality Overall Summary.pdf.

This amendment contains updated information for 140 mg and 180 mg strengths regarding to the solubility, permeability, and dissolution described in the Guidance for Industry: "Waiver of In-Vivo Bioavailability and Bioequivalence Studies Based on Biopharmaceutics Classification System".

Based on the data submitted in the original application, Barr proposed that temozolomide should be classified as a BCS Class I drug. The solubility, permeability, and dissolution data supporting our recommendation located in Module 5.3.1.2 in this amendment.

We are providing the analytical methods information copy in electronic format. This information is provided in two separate files labeled **Method Validation** and they are located in the **ANDA\Module 3\3.2.R Regional Information\3.2.R.3.P Method Validation Package Drug Product.pdf** and **3.2.R.3.S Method Validation Drug Substance.pdf** folder. *Barr commits to resolve any issues that may be identified in the enclosed method validation procedures during the review process or after approval.*

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 3/20/08 rev.9). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

Included in this electronic submission and in accordance with the Generic Drug Enforcement Act of 1992 are Debarment Certification Statements from Barr and its outside contractors. These are located in the folder: **ANDA\Module 1\1.3.3 debarment certification.pdf**. In addition to an electronic copy of the FDA form 356h (**ANDA\Module 1\ 1.1.2 FDA-356h.pdf**), this form has been provided in the original paper format.

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of Clinical Trials.gov Data Bank (42 U.S.C. § 282(j)) is provided in **ANDA\Module 1\FDA-3674.**

To aid in the review process, FDA's ANDA checklist for CTD or eCTD format for completeness and acceptability of an application for filing is also provided in **ANDA\Module 1\ anda_ectd_checklist.**

In accordance with 21 CFR Part 11.2(b) (2) and Docket 92S-0251 – Update Transmittal Memorandum 29, dated September 24, 2003, letters have been forwarded to the Baltimore and New York District Offices certifying that the electronic CMC section has been submitted to CDER and that the ORA District Office is able to access electronic CMC submissions through CDER's Electronic Document Room.

If you have any questions concerning this application, please contact Nicholas Tantillo at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director,
Regulatory Affairs

From: Shimer, Martin
Sent: Friday, March 21, 2008 12:43 PM
To: 'Tantillo, Nicholas'
Cc: 'Kraus, Heidi'; 'Kwok, William'; Shimer, Martin
Subject: RE: Authorization to use alternate means of providing notice

Nick,

It is permissible to use Fed Ex 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 in your New Strength Amendment to ANDA 78-879.

Sincerely,

Martin Shimer

From: Tantillo, Nicholas [mailto:NTantillo@barrlabs.com]
Sent: Friday, March 21, 2008 11:50 AM
To: Shimer, Martin
Cc: Kraus, Heidi; Kwok, William
Subject: Authorization to use alternate means of providing notice

Marty,
Today, March 21, 2008, or Monday, March 24, 2008 we hope to submit an amendment to our ANDA 78-879 for temozolomide capsules, to add the 140 mg and 180 mg strengths. The ANDA amendment contains a Paragraph IV patent certification. We are requesting authorization to use a courier service such as FedEx or UPS in addition to the U.S. Postal Service to provide the notice letters.

Regards,
Nick Tantillo
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
3/21/2008 02:42:18 PM
CSO

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

March 25, 2008

Electronic Submission

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

New Correspondence

REFERENCE: **ANDA 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Reference is also to Barr's electronic Amendment dated March 21, 2008 for the addition of Temozolomide Capsules, 140 mg and 180 mg strengths.

In the above referenced amendment, Barr has inadvertently omitted the word files for the CTD Summary Tables in Module 5 and the Draft Package Insert in Module 1.14. At this time, Barr is submitting the following word files in this correspondence:

- CTD Summary Tables (located in Module 5)
  Table 5 – 140mg.doc
  Table 5 – 180mg.doc
  Table 6.doc

- 1.14.1.3 Draft Package Insert.doc (located in Module 1)

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 3/24/08 rev. 5). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this application, please contact Nicholas Tantillo at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.

Thinh Duong FOR NICHOLAS TANTILLO

Nicholas Tantillo
Senior Director,
Regulatory Affairs

Telephone Fax

ANDA 78-879

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Barr Laboratories

TEL: 201-930-3650

ATTN: Nicholas Tantillo

FAX: 201-930-3318

FROM: Mrs. Angela Payne

Dear Sir:

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 Temozolomide Capsule.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 78-879 Date of Submission: 18 FEB 2008, 21 MAR 2008, and 25 MAR 2008

Applicant's Name: Barr laboratories

Established Name: Temozolomide Capsule 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

---

Labeling Deficiencies:

1. CONTAINER - 5s and 20s unit- of -use bottles- Satisfactory in FPL.

2. CARTONS (1s)- Satisfactory in FPL.

3. PROFESSIONAL INSERT-

   PRECAUTIONS, Pediatric subsection- Delete (b) (4) from the footnote section found following the table.

4. PATIENT INSERT - Satisfactory in draft.

5. PHARMACIST INFORMATION SHEET- Satisfactory in draft.

Revise your labels 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 and the latest approved labeling for the reference listed drug (or your last 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
4/8/2008 09:41:53 AM
for Wm Peter Rickman

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

April 16, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

LABELING AMENDMENT – ELECTRONIC SUBMISSION

REFERENCE: ANDA # 78-879
Temozolomide Capsules 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

Reference is made to our pending Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg.

Reference is also made to the Agency's comment letter dated April 8, 2008 requesting changes to the package brochure. The Container and Carton Labels were found satisfactory in Final Print.

Barr is now submitting the Final Printed Labeling for the package brochure as requested in the labeling comment letter as follows:

- Packaging Brochure 11001280 Revision APRIL 2008

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 4/14/2008 rev. 16). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this labeling amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 16, 2008

TO: Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence (HFD-650)

FROM: Sriram Subramaniam, Ph.D.
Xikui Chen, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. martin K. 4/16/08
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering ANDA 78-879, Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg, Sponsored by Barr Laboratories

At the request of the Office of Generic Drug (OGD), Division of Bioequivalence (DBE), the Division of Scientific Investigations audited the following *in vitro* permeability studies, submitted as part of biopharmaceutical classification system (BCS) biowaiver.

Report 7BARRP1R1GLPS34:	In Vitro Permeability Study of Temozolomide According to the Biopharmaceutical Classification System (BCS) Guidelines Issued by the United States Food and Drug Administration
Report 7BARRP1R1GLPS34 (Appendix 1):	Validation of an LC/MS Method for Temozolomide Permeability Samples, SOP (b) (4) -013-G
Study 6 (b) (4) BCSval:	Revalidation of the Caco-2 System for BCS *In Vitro* Permeability Studies

The *in vitro* studies were submitted to support a biowaiver request in accordance with CDER's BCS guidance*. The guidance allows biowaivers for immediate-release oral dosage forms that exhibit **high** solubility and **high** permeability with **rapid** dissolution (i.e. Class I drug).

The *in vitro* permeability study and the associated validation studies were conducted at (b) (4) (b) (4). Caco-2 cell monolayers were used to assess the apparent permeability (Papp) of temozolomide.

A Form 483 was issued to (b) (4) at the conclusion of the inspection (b) (4). Our evaluation of the significant findings and the firm's response follows:

(b) (4)

* CDER's Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutical Classification System. (August 2000)

Following this page, 2 pages withheld in full (b)(4)

(b) (4)

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Xikui Chen, Ph.D.

Sriram Subramaniam, Ph.D.

Final Classification:
VAI – (b) (4)

cc:
HFD-45/RF
HFD-45/Vaccari
HFD-48/Subramaniam/Chen/ Himaya/CF
HFD-650/Munshi/Suh
HFR-CE1505/Despins
Draft: XC 2/26/08
Edit: SS 3/27/08
DSI: (b) (4) O:\BE\EIRCOVER\78879bar tem doc
FACTS ID: (b) (4)

Following this page, 7 pages withheld in full (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/

Xikui Chen
4/17/2008 01:57:56 PM
COMPLIANCE OFFICER
Hard copy signed by Dr. Yau for Dr. Viswanathan

Sriram Subramaniam
4/17/2008 02:00:55 PM
PHARMACOLOGIST

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 : April 24, 2007

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 78-879 for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 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 78-879 for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 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 Marrch 19, 2007 for its Temozolomide 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
4/22/2008 10:28:21 AM
APPLICATIONS EXA

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 : April 21, 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 78-879 for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 250 mg, 140 mg, and 180 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv). **The first generic and new strength products are 140 mg and 180 mg.**

Barr Laboratories Inc. has submitted ANDA 78-879 for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 250 mg, 140 mg, and 180 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 March 21, 2008 for its Temozolomide 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".

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/s/

Eda Howard
5/14/2008 02:49:42 PM
APPLICATIONS EXA

From: Shimer, Martin
Sent: Friday, March 21, 2008 12:43 PM
To: 'Tantillo, Nicholas'
Cc: 'Kraus, Heidi'; 'Kwok, William'; Shimer, Martin
Subject: RE: Authorization to use alternate means of providing notice

Nick,

It is permissible to use Fed Ex 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 in your New Strength Amendment to ANDA 78-879.

Sincerely,

Martin Shimer

From: Tantillo, Nicholas [mailto:NTantillo@barrlabs.com]
Sent: Friday, March 21, 2008 11:50 AM
To: Shimer, Martin
Cc: Kraus, Heidi; Kwok, William
Subject: Authorization to use alternate means of providing notice

Marty,
Today, March 21, 2008, or Monday, March 24, 2008 we hope to submit an amendment to our ANDA 78-879 for temozolomide capsules, to add the 140 mg and 180 mg strengths. The ANDA amendment contains a Paragraph IV patent certification. We are requesting authorization to use a courier service such as FedEx or UPS in addition to the U.S. Postal Service to provide the notice letters.

Regards,
Nick Tantillo
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 07:33:09 AM
CSO

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

June 19, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attn: Joe Wetzel

GRATUITOUS AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to Barr Laboratories Inc.'s, ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007 for the 5 mg, 20 mg, 100 mg and 250 mg strengths and Amendment to the pending Application dated March 21, 2008 for the 140 mg and 180 mg strengths submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to Barr's Minor Amendment dated March 17, 2008 in response to the Agency's comment deficiency letter dated November 7, 2007.

Barr is now accepting the Agency's proposal to include a Test for Microbial Limits (USP <61>) in the drug product specifications. Barr will perform microbial testing on all strengths at the release stage and at the end of the shelf life. The Analytical Test Method (MTH- 826 version 8.0), Finished Product Analytical Specifications & Test Records and the Marketed Product Stability Specifications Sheet & Test Records have been updated for all strengths to include Test for Microbial Limits and were included in the above referenced Amendments.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's Antivirus Corporate Edition Software (version 6/18/08 rev. 3). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this labeling amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

June 19, 2008

Otto Vitillo
District Director
Food and Drug Administration
158-15 Liberty Avenue
Second Floor
Jamaica, New York 11433

GRATUITOUS AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Pursuant to 21 CFR Part 11.2(b) (2), and the Office of Regulatory Affairs (ORA) Update Transmittal Memorandum 29 to Docket 92S-0251 dated September 24, 2003, Barr Laboratories, Inc. is certifying that an Electronic Gratuitous Amendment filed under section 505 (j) of the Federal Food and Cosmetic Act for Temozolomide Capsules, 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250mg has been submitted to the Center for Drug Evaluation and Research (CDER).

Therefore, sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room.

If you have any questions concerning this application, please contact me at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director
Regulatory Affairs

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

June 19, 2008

Brooke Seeman
Virginia CSO
Pre-Approval – New Product
Food and Drug Administration
6000 Metro Drive, S.101
Baltimore, Maryland 21215

GRATUITOUS AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Pursuant to 21 CFR Part 11.2(b) (2), and the Office of Regulatory Affairs (ORA) Update Transmittal Memorandum 29 to Docket 92S-0251 dated September 24, 2003, Barr Laboratories, Inc. is certifying that an Electronic Gratuitous Amendment filed under section 505 (j) of the Federal Food and Cosmetic Act for Temozolomide Capsules, 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250mg has been submitted to the Center for Drug Evaluation and Research (CDER).

Therefore, sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room.

If you have any questions concerning this application, please contact me at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director
Regulatory Affairs

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 #: 78-879 **FIRM NAME**: BARR LABORATORIES INC.

PIV: YES **Electronic or Paper Submission:** ECTD FORMAT (ELECTRONIC DATA)

RELATED APPLICATION(S):

First Generic Product Received? YES ON 140 MG AND 180MG (BCS CLASS I PRODUCT)

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DRUG NAME: TEMOZOLOMIDE

DOSAGE FORM: CAPSULES, 5 MG, 20 MG, 100 MG, 250 MG, 140 MG AND 180 MG

NEW STRENGTH AND FIRST GENERIC ON 140 MG AND 180 MG

Random Queue: 2

Chem Team Leader: Smela, Michael CHEM PM: Esther Chuh Labeling Reviewer: Angela Payne
BIO PM: Beth Fabian-Fritsch

Letter Date: MARCH 21, 2008 **Received Date**: MARCH 24, 2008

Comments: EC- 3+2=5 YES **On Cards:** YES
Therapeutic Code: 5010100 CYTOXIC

Archival copy: ECTD FORMAT ELECTRONIC DATA **Sections** I
Review copy: NA 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 Saundra T. Middleton	**Recommendation:**
Date 7/9/2008	☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
First generic for these strength was not looked at by DBE since a BCS class I waiver request was granted for the original strengths submitted March 19, 2007 and the same is submitted for this one.

Barr did not submit a detail QQS. 7/9/2008 Barr was asked today to submit this in detail in the interim (see below).

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: MARCH 21, 2008	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
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) or Disclosure Statement (Form FDA 3455) NA Form FDA 3674 was submitted	☐

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) PIV 5'260'291
2. Paragraph: (Check all certifications that apply)
   MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒
   No Relevant Patents ☐
3. Expiration of Patent(s): 2/11/2014
   a. Pediatric exclusivity submitted?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES did not include ODE or I-450 in labeling

Patent and Exclusivity Search Results from query on Appl No 021029 Product 006 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
021029	006	5260291	Aug 11, 2013	Y	Y	U-619	
021029	006	5260291*PED	Feb 11, 2014				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021029	006	I-450	Mar 15, 2008
021029	006	ODE	Mar 15, 2012

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-619	TREATMENT OF MALIGNANT NEOPLASM

Exclusivity Codes

This page defines the exclusivity codes.

Code	Definition
ODE	ORPHAN DRUG EXCLUSIVITY

Code	Definition
I-450	TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED HIGH GRADE GLIOMAS CONCOMITANTLY WITH RADIOTHERAPY AND THEN AS ADJUVANT TREATMENT

1.12.12 Comparison Between Generic Drug and RLD-505(j)(2)(A)

3. Comparison of the Generic Drug versus Reference Listed Drug

Manufacturer:	Schering-Plough Corporation	**Barr Laboratories, Inc.**
Drug Name:	Temodar® (Temozolomide) Capsules	Temozolomide Capsules
1. Conditions for Use	Temodar® capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. Temodar® capsules also are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.	Temozolomide capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

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 YES - # (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒
1.12.11	**Basis for Submission** NDA# : 21-029 Ref Listed Drug: TEMODAR Firm: SCHERING-PLOUGH CORPORATION 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 does not include I-450 (firm was asked to revised labeling to not include I-450)
2. Active ingredients YES
3. Inactive ingredients YES
4. Route of administration YES
5. Dosage Form YES
6. Strength YES

3. Comparison of the Generic Drug versus Reference Listed Drug

Manufacturer:	Schering-Plough Corporation	**Barr Laboratories, Inc.**
Drug Name:	Temodar® (Temozolomide) Capsules	Temozolomide Capsules
1. Conditions for Use	Temodar® capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. Temodar® capsules also are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.	Temozolomide capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

1.12.14 **Environmental Impact Analysis Statement** YES ☒

1.12.15 **Request for Waiver** ☒
Request for Waiver of In-Vivo BA/BE Study(ies): Electronic, YES BCS (SEE BELOW)

1.14.1 **Draft Labeling (Mult Copies N/A for E-Submissions)** ☐

1.14.1.1
4 copies of draft (each strength and container) YES

1.14.1.2
1 side by side labeling comparison of containers and carton with all differences annotated and explained YES

1.14.1.3
1 package insert (content of labeling) submitted electronically YES
***Was a proprietary name request submitted? NO
(If yes, send email to Labeling Reviewer indicating such.)

INDICATIONS AND USAGE

(b) (4)

~~TEMODAR~~Temozolomide Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

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 YES **1.14.3.3** 1 RLD label and 1 RLD container label YES 5 AND 20 COUNT EACH	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: PDF (archive) _ YES ___ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _____ YES __X____ NO – Barr referenced their original submission of March 19, 2007 – Barr was asked to submit this in the interim.** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) YES** **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 YES** **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) NO** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☐

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature YES** **3.2.S.1.2** **Structure YES** **3.2.S.1.3** **General Properties YES**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES # (b) (4) 4. CFN or FEI numbers YES	☒
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) YES **3.2.S.4.2** **Analytical Procedures** YES **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) YES **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **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 YES 2) Inactive ingredients are appropriate per IIG YES – SEE BELOW	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report YES	☒
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) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation YES **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES – SEE BELOW 3. If sterile product: Aseptic fill / Terminal sterilization YES 4. Reprocessing Statement YES **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation - NA** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒

Following this page, 1 page withheld in full (b)(4)

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** YES Source of inactive ingredients identified YES **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **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 YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** YES **3.2.P.5.2** **Analytical Procedures** YES **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers YES **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **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) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes YES 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – 24 MONTHS **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch YES	☒

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)** YES **3.2.R.2.S** **Comparability Protocols** YES **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3
3.2.R Regional Information

ACCEPTABLE

ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg
Amendment for the addition of 140 mg and 180 mg

3.2.R REGIONAL INFORMATION

3.2.R.1.P.1 Executed Batch Records

3.2.R.1.P.1.2 Packaging

(b) (4)

[redacted]

3.2.R REGIONAL INFORMATION

3.2.R.1.P.1 Executed Batch Records

3.2.R.1.P.1.2 Packaging

(b) (4)

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 YES – SEE BELOW **3.2.R.1.P.2** **Information on Components** NO **3.2.R.2.P** **Comparability Protocols NO** **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)	☒

ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg
Amendment for the addition of 140 mg and 180 mg

3.2.R REGIONAL INFORMATION

3.2.R.1.P.1 Executed Batch Records

3.2.R.1.P.1.2 Packaging

(b) (4)

[redacted]

(b) (4)

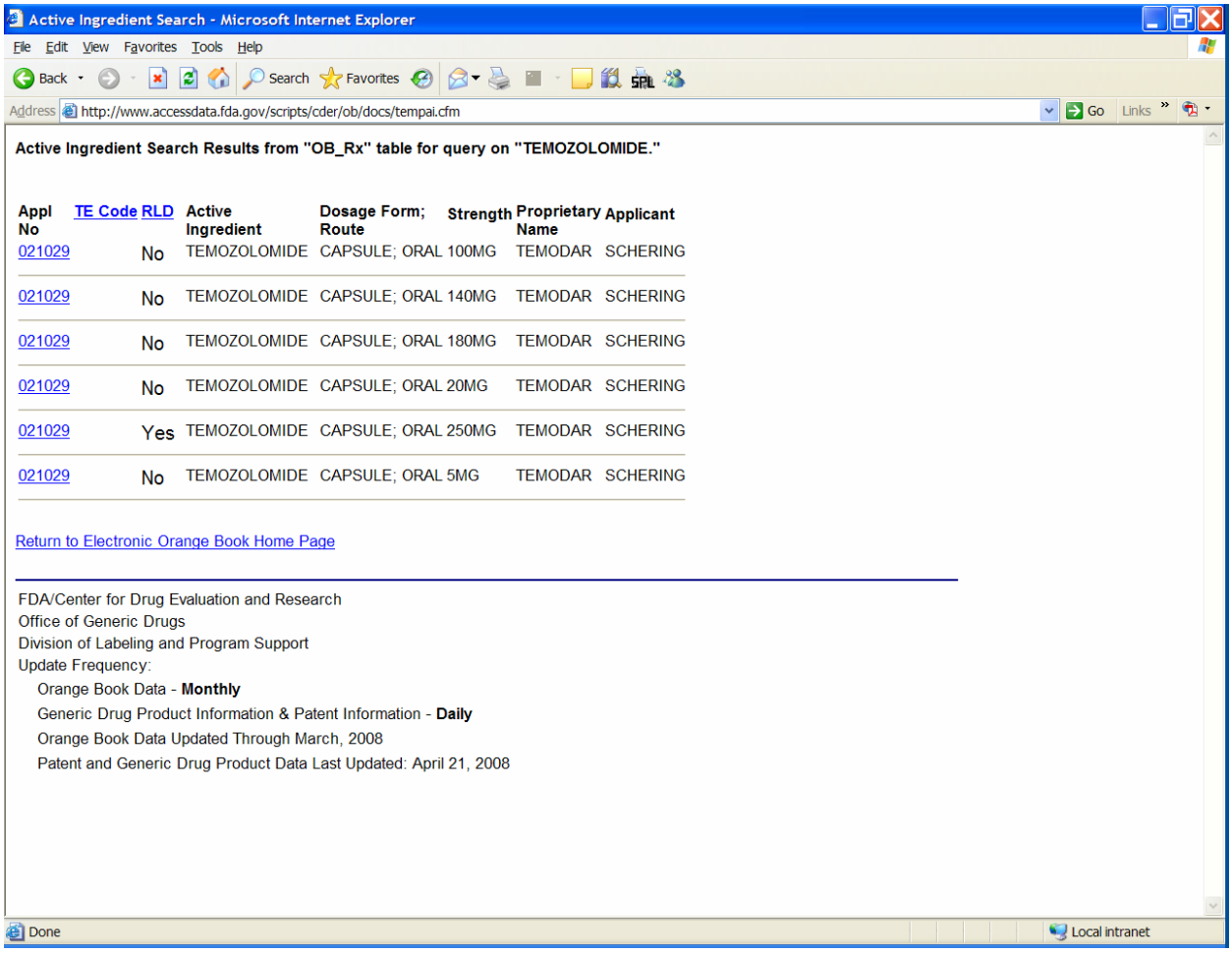
MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
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: IN-VIVO PK STUDY(IES)** (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)NA 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study NA Table 7. Incidence of Adverse Events in Individual Studies NA Table 8. Reanalysis of Study Samples NA **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports – BCS CLASS I WAIVER REQUEST ACCEPTED SEE DBE CHECKLIST IN DFS** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies YES Table 5. Formulation Data YES **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation NA **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) NA 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: NO	☐
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** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 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% or 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, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 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 - Microsoft Internet Explorer

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Go Links

Active Ingredient Search Results from "OB_Rx" table for query on "TEMOZOLOMIDE."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021029		No	TEMOZOLOMIDE	CAPSULE; ORAL	100MG	TEMODAR	SCHERING
021029		No	TEMOZOLOMIDE	CAPSULE; ORAL	140MG	TEMODAR	SCHERING
021029		No	TEMOZOLOMIDE	CAPSULE; ORAL	180MG	TEMODAR	SCHERING
021029		No	TEMOZOLOMIDE	CAPSULE; ORAL	20MG	TEMODAR	SCHERING
021029		Yes	TEMOZOLOMIDE	CAPSULE; ORAL	250MG	TEMODAR	SCHERING
021029		No	TEMOZOLOMIDE	CAPSULE; ORAL	5MG	TEMODAR	SCHERING

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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 March, 2008
Patent and Generic Drug Product Data Last Updated: April 21, 2008

Done

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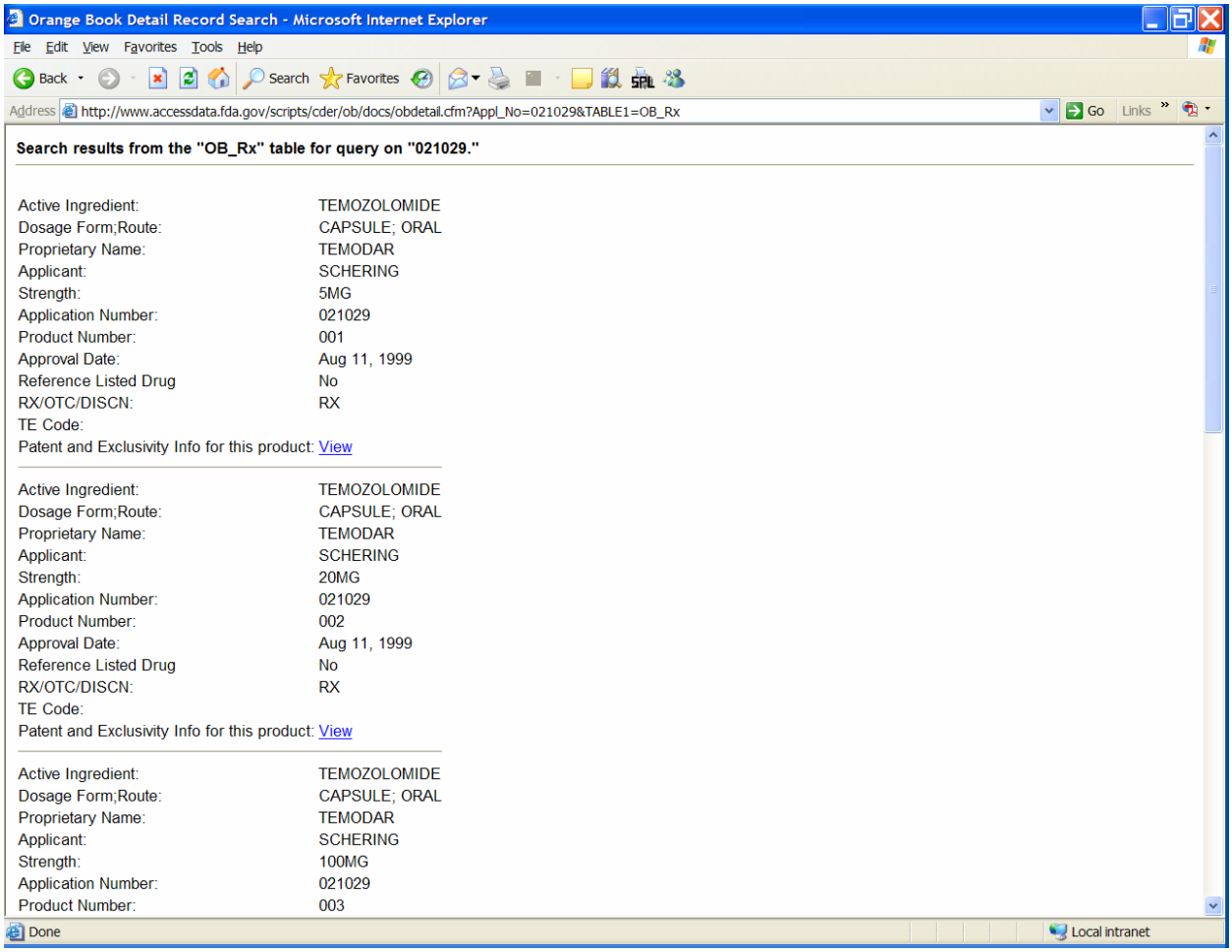

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021029&TABLE1=OB_Rx

Go Links

Search results from the "OB_Rx" table for query on "021029."

Active Ingredient: TEMOZOLOMIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: TEMODAR
Applicant: SCHERING
Strength: 5MG
Application Number: 021029
Product Number: 001
Approval Date: Aug 11, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View

Active Ingredient: TEMOZOLOMIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: TEMODAR
Applicant: SCHERING
Strength: 20MG
Application Number: 021029
Product Number: 002
Approval Date: Aug 11, 1999
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View

Active Ingredient: TEMOZOLOMIDE
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: TEMODAR
Applicant: SCHERING
Strength: 100MG
Application Number: 021029
Product Number: 003

Done

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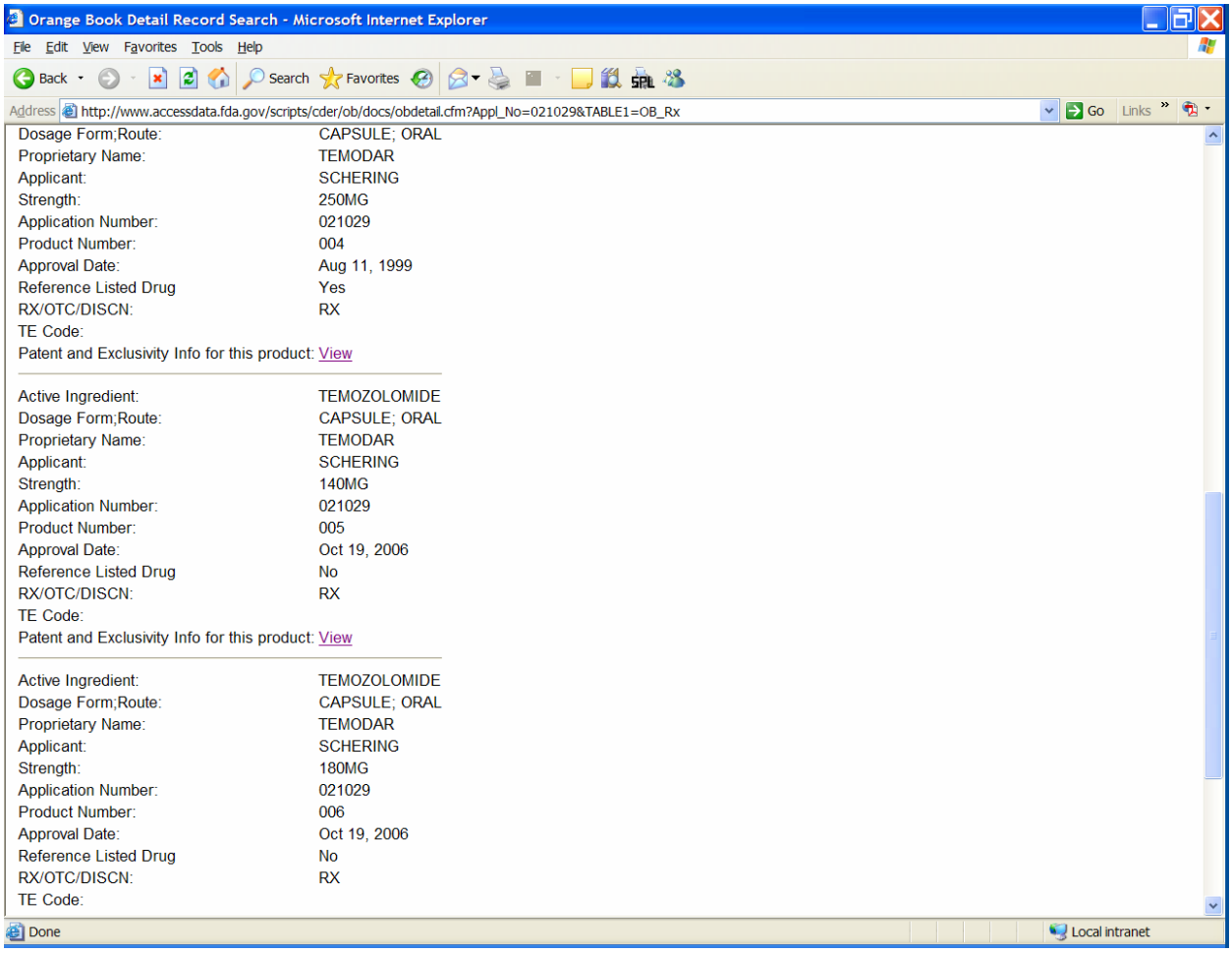

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=021029&TABLE1=OB_Rx

Go Links

Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	TEMODAR
Applicant:	SCHERING
Strength:	250MG
Application Number:	021029
Product Number:	004
Approval Date:	Aug 11, 1999
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TEMOZOLOMIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	TEMODAR
Applicant:	SCHERING
Strength:	140MG
Application Number:	021029
Product Number:	005
Approval Date:	Oct 19, 2006
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	TEMOZOLOMIDE
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	TEMODAR
Applicant:	SCHERING
Strength:	180MG
Application Number:	021029
Product Number:	006
Approval Date:	Oct 19, 2006
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

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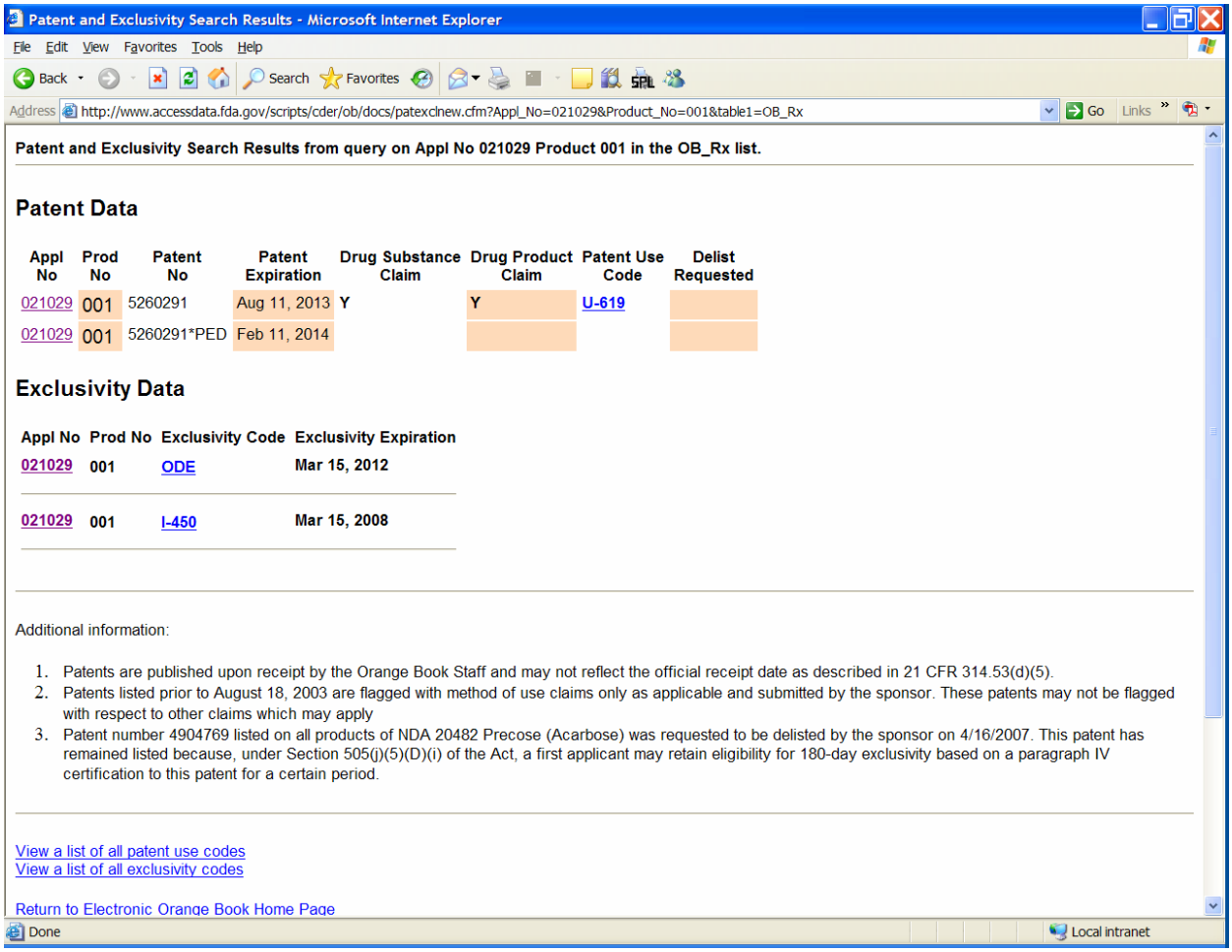

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021029&Product_No=001&table1=OB_Rx

Go Links

Patent and Exclusivity Search Results from query on Appl No 021029 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
021029	001	5260291	Aug 11, 2013	Y	Y	U-619	
021029	001	5260291*PED	Feb 11, 2014				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021029	001	ODE	Mar 15, 2012
021029	001	I-450	Mar 15, 2008

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
3. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021029&Product_No=002&table1=OB_Rx

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Patent and Exclusivity Search Results from query on Appl No 021029 Product 002 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
021029	002	5260291	Aug 11, 2013	Y	Y	U-619	
021029	002	5260291*PED	Feb 11, 2014				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021029	002	I-450	Mar 15, 2008
021029	002	ODE	Mar 15, 2012

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
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3. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

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Patent and Exclusivity Search Results from query on Appl No 021029 Product 004 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
021029	004	5260291	Aug 11, 2013	Y	Y	U-619	
021029	004	5260291*PED	Feb 11, 2014				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021029	004	ODE	Mar 15, 2012
021029	004	I-450	Mar 15, 2008

Additional information:

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2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
3. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

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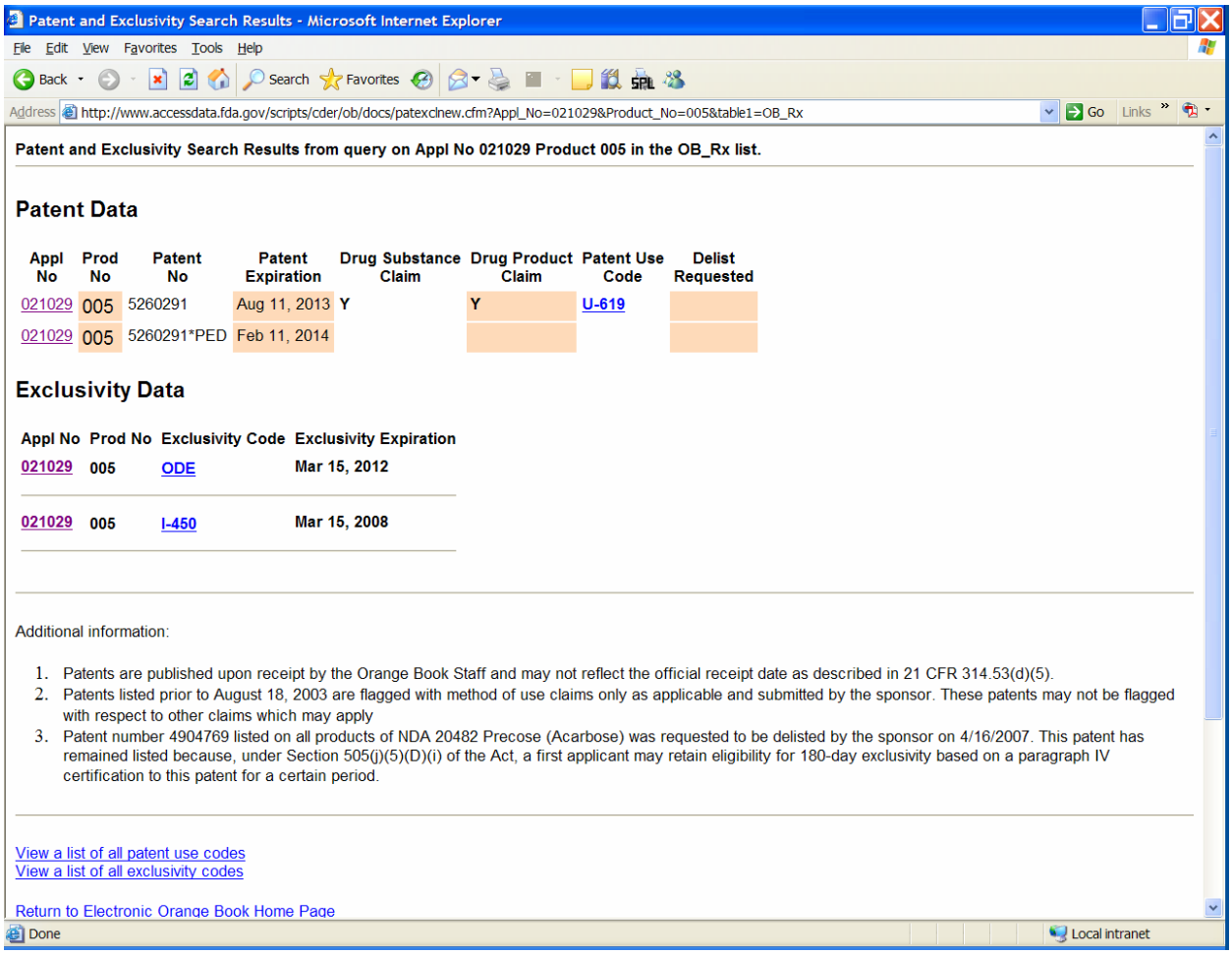

Patent and Exclusivity Search Results from query on Appl No 021029 Product 005 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021029	005	5260291	Aug 11, 2013	Y	Y	U-619	
021029	005	5260291*PED	Feb 11, 2014				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021029	005	ODE	Mar 15, 2012
021029	005	I-450	Mar 15, 2008

Additional information:

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3. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

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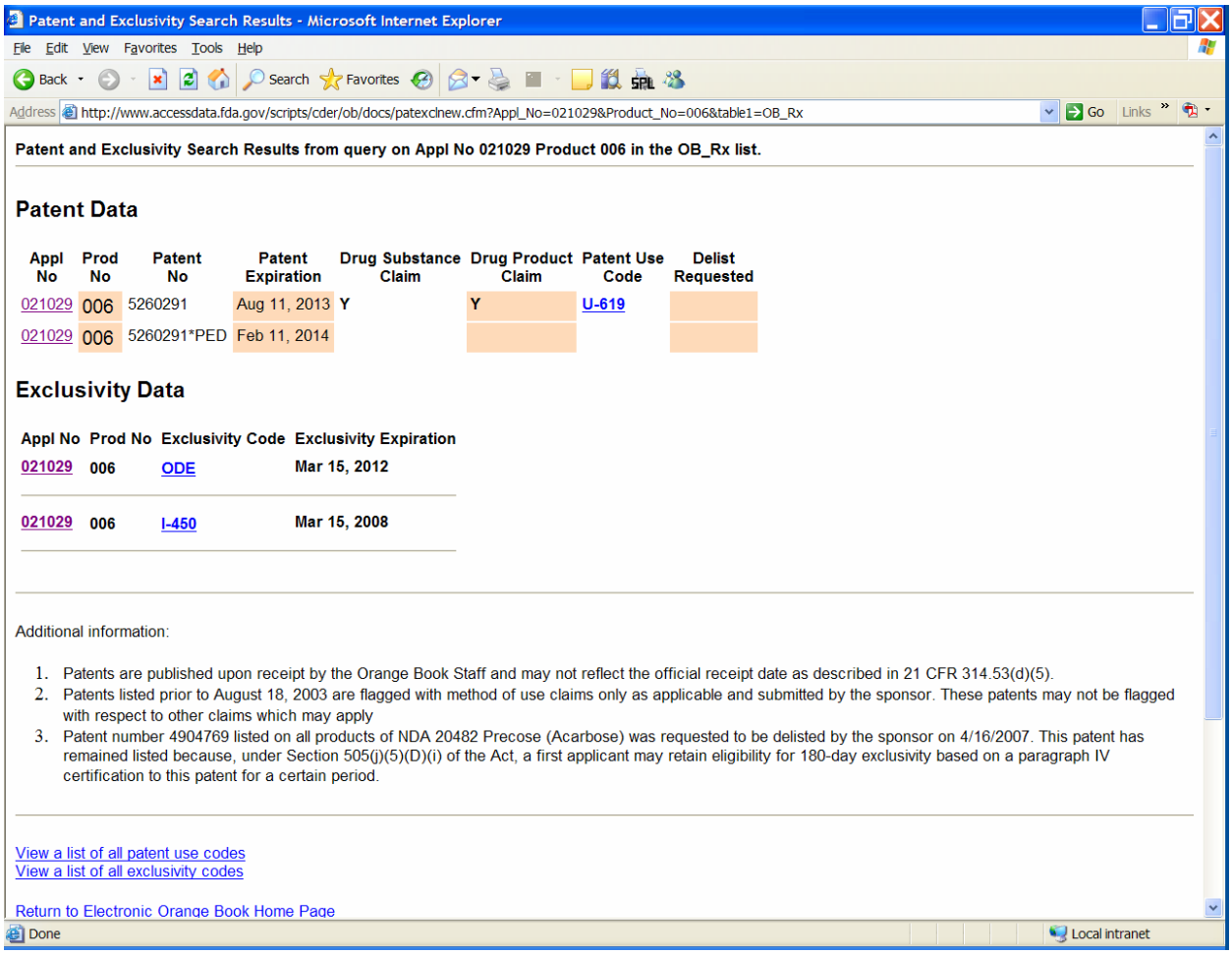
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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021029&Product_No=006&table1=OB_Rx
Go Links
Patent and Exclusivity Search Results from query on Appl No 021029 Product 006 in the OB_Rx list.
Patent Data
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested
021029 | 006 | 5260291 | Aug 11, 2013 | Y | Y | U-619 |
021029 | 006 | 5260291*PED | Feb 11, 2014 | | | |
Exclusivity Data
Appl No | Prod No | Exclusivity Code | Exclusivity Expiration
021029 | 006 | ODE | Mar 15, 2012
021029 | 006 | I-450 | Mar 15, 2008
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
3. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.
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/s/

Martin Shimer

7/16/2008 01:02:32 PM

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

August 6, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attn: Joe Wetzel

TELEPHONE AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to Barr Laboratories Inc.'s, ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007 for the 5 mg, 20 mg, 100 mg and 250 mg strengths and the Amendment dated March 21, 2008 for the addition of the 140 mg and 180 mg strengths submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation between Ms. Saundra Middleton of the FDA, OGD and Mr. William Kwok of Barr on July 9, 2008. Ms. Middleton asked Barr to provide an updated QOS for the referenced amendment dated March 21, 2008 and submit this as a Telephone Amendment.

Barr has updated the QOS to include information pertaining to Temozolomide Capsules, 140 mg and 180 mg strengths.

- Updated QOS is located in **Module 2.3**

In addition, Barr is also providing the following updates in this amendment:

USP General Chapter <467> requirement

Regarding the current USP General Chapter <467> requirement, Barr is submitting information for each ingredient (drug substance and excipients) used in the formulation of Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg.

Based on the data from the manufacturers of the active pharmaceutical ingredient and excipients, the maximum quantities of residual solvents that could appear in Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg were calculated and the maximum quantities meets ICH Q3C requirements. Furthermore, Barr performed the calculations for the drug products to demonstrate that the levels of residual solvents are within the safety recommendations of USP General Chapter <467> for residual solvents.

Enclosed please find the following calculation worksheets for Class 2 and Class 3 residual solvents for each ingredient (drug substance and excipients) used in the drug product formulations.

- Residual Solvent Calculation Worksheets for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg located in **Module 3.2.P.5**

Updated Stability data for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Barr is also providing the following reports in this amendment:

- Updated Stability Reports with up to 18 M long term data for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg located in **Module 3.2.P.8**
- Updated Stability Reports with up to 6 M long term data for Temozolomide Capsules, 140 mg, and 180 mg located in **Module 3.2.P.8**

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's Antivirus Corporate Edition Software (version 08/05/08 rev.3). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions concerning this telephone amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

Tristan Duong (for)

Nicholas Tantillo
Senior Director, Regulatory Affairs

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

August 6, 2008

Otto Vitillo
District Director
Food and Drug Administration
158-15 Liberty Avenue
Second Floor
Jamaica, New York 11433

TELEPHONE AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Pursuant to 21 CFR Part 11.2(b) (2), and the Office of Regulatory Affairs (ORA) Update Transmittal Memorandum 29 to Docket 92S-0251 dated September 24, 2003, Barr Laboratories, Inc. is certifying that an Electronic Telephone Amendment filed under section 505 (j) of the Federal Food and Cosmetic Act for Temozolomide Capsules, 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250mg has been submitted to the Center for Drug Evaluation and Research (CDER).

Therefore, sponsors submitting electronic submissions to CDER do not need to submit an electronic submission or paper submission to the ORA District Office. District Offices are able to access electronic Chemistry Manufacturing and Control submissions through CDER's Electronic Document Room.

If you have any questions concerning this application, please contact me at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Thristal Duong (FOR)

Nicholas Tantillo
Senior Director
Regulatory Affairs

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

August 6, 2008

Brooke Seeman
Virginia CSO
Pre-Approval – New Product
Food and Drug Administration
6000 Metro Drive, S.101
Baltimore, Maryland 21215

TELEPHONE AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Pursuant to 21 CFR Part 11.2(b) (2), and the Office of Regulatory Affairs (ORA) Update Transmittal Memorandum 29 to Docket 92S-0251 dated September 24, 2003, Barr Laboratories, Inc. is certifying that an Electronic Telephone Amendment filed under section 505 (j) of the Federal Food and Cosmetic Act for Temozolomide Capsules, 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250mg has been submitted to the Center for Drug Evaluation and Research (CDER).

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If you have any questions concerning this application, please contact me at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Thritun Duong (For)

Nicholas Tantillo
Senior Director
Regulatory Affairs

COMPLETE RESPONSE -- MINOR

ANDA 78-879

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: Rosalyn Adigun FDA CONTACT PHONE: (240) 276-8518

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 19, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg,140 mg, 180 mg, and 250 mg.

Reference is also made to your amendments dated March 17. March 21, March 25, June 19, and August 6, 2008.

SPECIAL INSTRUCTIONS: See CMC comments provided

Please submit your response in electronic format. 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 (__2__ 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.

Chemistry Comments to be provided to the Applicant

ANDA: 78-879 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. Please revise and submit your drug product release specifications to include a *"Residual Solvents Test"* with test specifications listed as "Complies with USP <467>".

2. (b) (4)

3.

4.

5. Please provide your revised drug product COAs and your stability data sheets with actual data to reflect the above revisions.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available drug product room temperature stability data.

2. Labeling deficiencies were communicated to you via facsimile on May 8, 2008. You should address the issues in the May 8, 2008 communication prior to or concurrent with your response to this communication.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry 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/

James Fan
11/13/2008 01:52:27 PM
James M Fan for Rashmikant Patel

Barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645-1523

December 15, 2008

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Bioequivalence - Telephone Amendment

REFERENCE: ANDA # 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg strengths and Amendment to the pending Application dated March 21, 2008 for the addition of the 140 mg and 180 mg strengths submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation between Ms. Nam Chun of the FDA, ODG and Ms. Linda O'Dea of Barr on November 3, 2008. Ms. Chun asked Barr to provide dissolution profiles on 12 dosage units each of test and reference products for Temozolomide Capsules 5 mg, 20 mg, 100 mg, 140 mg and 180 mg generated using Barr's proposed method in media of various pHs (pHs 1.2, 4.5 and 6.8 buffer). Ms. Chun said to submit this information as a telephone amendment.

Response:

As per the agency's request, the dissolution testing was conducted on Barr's Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg and 180 mg and corresponding reference products. The report is located in **Module 5.3.1.2 Study Summary for Dissolution Studies.**

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 12/14/08 rev.3). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

If you have any questions concerning this amendment, please contact me at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

BIOEQUIVALENCE AMENDMENT

ANDA 78-879

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, Sr. FAX: 201-930-3318

FROM: Diana Solana-Sodeinde FDA CONTACT PHONE: (240)276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on March 19, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg.

Reference is also made to your amendment dated August 23, 2007; October 5, 2007; March 21, 2008 and December 15, 2008.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** 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 "Bioequivalence 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.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

ANDA: 78-879

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Temozolomide Capsules,
5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

The Division of Bioequivalence has completed its review and has identified the following deficiencies:

1. For your Permeability Study (Study Report No.7BARRP1R1GLPS34), the pH of the apical compartment (top well) was 6.5 and the pH of the basolateral compartment (bottom well) was 7.4. Please provide a detailed justification for using two different pHs to conduct your permeability study.

2. Also, in your Permeability Study report (Study Report No. 7BARRP1R1GLPS34), you provided the percent recovery in the top and bottom wells at pH 6.5 for Temozolomide. However, you did not provide the percent recovery of Temozolomide (0.01 µM) in the top and bottom wells at pH 7.4. Therefore, please submit the percent recovery (and % coefficient of variation) of Temozolomide (0.01 µM) at pH 7.4.

3. For future submissions, please establish acceptable criteria (including number of data points used in the linearity regression) for estimating rate of change of receiver concentration (*dCr/dt*) in the calculation of the apparent permeability (*Papp*). Please use a minimum of three points to calculate the slope of the line for low, medium, and high permeability drug substances.

4. For future submissions, please establish acceptable criteria for reporting percent recovery for permeability experiments in your Standard Operating Procedures (SOPs).

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

1/27/2009 02:29:59 PM

barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645 • 201-930-3300

February 3, 2009

Off ice of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT CORRESPONDENCE

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg.

Reference is also made to Barr Laboratories Inc.'s, ('Barr') electronic Amendment to a pending Abbreviated New Drug Application dated March 21, 2008, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for two (2) additional strengths of Temozolomide Capsules, 140 mg and 180 mg.

In accordance with our Patent Certification Statement submitted in Module 1, Section 1.3.5.2 of the above referenced original application and 21 CFR §314.95(a), the notice for the 140 mg and 180 mg strengths with respect to U.S. Patent No. 5,260,291 was sent by certified mail on March 24, 2008, return receipt requested to the owner of the patent which is the subject of the certification and to the holder of the approved application under Section 505(b) of the Act.

In accordance with 21 CFR §314.95(b), Barr is hereby submitting a Correspondence to certify that notices for the 140 mg and 180 mg strengths were provided to Schering – Plough Corporation (approval holder of New Drug Application ("NDA") No. 21-029, Cancer Research Technology Limited and Cancer Research Technology Inc. (owners of U.S. Patent No. 5,260,291) by Sterne, Kessler, Goldstein and Fox P.L.L.C on behalf of Barr.

The contents of the notice letter comply with 21 CFR §314.95(c). The notice letter cites the appropriate section of the Act. In the notice letter, Barr alleges that in its opinion U.S. Patent No. 5,260,291 is invalid, unenforceable or will not be infringed by the manufacture, use, or sale of Barr's Temozolomide Capsules, 140 mg and 180 mg.

barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645 • 201-930-3300

In accordance with 21 CFR §314.95(e), enclosed please find a copy of the signed return receipts and FedEx delivery confirmation from Schering –Plough Corporation, and Cancer Research Technology Inc. for the notice, which was delivered on March 26, 2008 and March 28, 2008 respectively.

Attached also find the FedEx delivery confirmation for Cancer Research Technology Limited, which was delivered on March 26, 2008.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 2/2/09 rev. 7). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

Please note that Barr Laboratories, Inc is an indirectly, wholly-owned subsidiary of Teva Pharmaceuticals, USA.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645 • 201-930-3300

February 6, 2009

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCY- TELEPHONE AMENDMENT

REFERENCE: **ANDA 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to our Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg** strengths and the Amendment dated March 21, 2008 for the addition of the **140 mg and 180 mg strengths**.

Reference is also made to the Agency's January 27, 2009 letter in which the Agency had the following comments. Reference is also made to the telephone message from Ms. Diana Solana-Sodeinde of the FDA, ODG on February 6, 2009, and Ms. Sodeinde said to submit this amendment as a telephone amendment.

Comment 1:

For your Permeability Study (Study Report NO. 7BARRP1R1GLPS34), the pH of the apical compartment (top well) was 6.5 and the pH of the basolateral compartment (bottom well) was 7.4. Please provide a detailed justification for using two different pHs to conduct your permeability study.

Response 1:

The data to address this request were already included in our Abbreviated New Drug Application dated March 19, 2007 and subsequent amendment dated March 21, 2008. As per your request, a detailed justification is provided using the information that was included in our ANDA.

(b) (4)

Following this page, 2 pages withheld in full (b)(4)

Comment 2:

Also, in your Permeability Study report (Study Report No. 7BARRP1R1GLPS34), you provided the percent recovery in the top and bottom wells at pH 6.5 for Temozolomide. However, you did not provide the percent recovery of Temozolomide (0.01 µM) in the top and bottom wells at pH 7.4. Therefore, please submit the percent recovery (and % coefficient of variation) of Temozolomide (0.01 µM) at pH 7.4.

Response 2:

The percent recoveries of Temozolomide from the top and bottom wells were determined at both pH 6.5 and pH 7.4 and the data were submitted in our Permeability Study report (Study Report No. 7BARRP1R1GLPS34).

At pH 6.5, the recoveries were 92.9 ± 3.00 % and 102 ± 3.58 % from the top and bottom chambers, respectively. At pH 7.4, the recoveries were 84.7 ± 2.30 % and 92.3 ± 2.39 % from the top and bottom chambers, respectively.

Please note that the recoveries results of Temozolomide from the top and bottom wells were included in Tables A10 and A11, which was located on pages 33 and 34 of Study Report No. 7BARRP1R1GLPS34 (see Module 5.3, pages 47 and 48 of our Abbreviated New Drug Application dated March 19, 2007 for additional details).

Comment 3:

For future submissions, please establish acceptable criteria (including number of data points used in the linearity regression) for estimating rate of change of receiver concentration (*dCr/dt*) in the calculation of the apparent permeability (Papp). Please use a minimum of three points to calculate the slope of the line for low, medium and high permeability drug substances.

Comment 4:

For future submissions, please establish acceptable criteria for reporting percent recovery for permeability experiments in your Standard Operating Procedures (SOPs).

Responses 3 and 4:

Barr acknowledges the above comments and recommendations.

Barr declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software

(version 2/4/09 revision 21). Barr also declares that all original signed paper certifications have been provided in the original paper format.

Lastly, please note that Barr Laboratories, Inc is an indirectly, wholly-owned subsidiary of Teva Pharmaceuticals, USA.

If you have any questions concerning this correspondence, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs
Barr Laboratories, Inc is an
indirectly, wholly-owned subsidiary
of Teva Pharmaceuticals, USA

barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645 • 201-930-3300

February 6, 2009

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773.

MINOR AMENDMENT

REFERENCE: **ANDA 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to our Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg** strengths and the Amendment dated March 21, 2008 for the addition of the **140 mg and 180 mg strengths**.

Reference is also made to the Agency's November 13, 2008 letter in which the Agency had the following comments. The Agency indicated that Barr's response would be considered a MINOR AMENDMENT.

A. The deficiencies presented below represent Minor deficiencies.

Comment 1:

Please revise and submit your drug product release specifications to include a *"Residual Solvents Test"* with test specifications listed as "Complies with USP <467>".

Response 1:

The Finished Product Specifications sheets have been revised to add a statement stating that the finished products comply with the requirements of USP <467>, Option 2 limit. The revised specifications sheets are provided in **Module 3.2.P.5 Control of Drug Product**.

Following this page, 3 pages withheld in full (b)(4)

Comment 5:

Please provide your revised drug product COAs and your stability data sheets with actual data to reflect the above revisions.

Response 5:

The revised drug product release and stability specifications and test records are enclosed in this amendment. Please see Special Studies report, ARD_RPT_2518 Version 2.0 located in **Module 3.2.P.8 Stability** for the actual data to reflect the changes listed in this amendment.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

Comment 1:

Please provide all available drug product room temperature stability data.

Response 1:

Barr is providing the following reports in this amendment:

- Updated Stability Reports with up to **24 M long term data** for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg located in Module 3.2.P.8
- Updated Stability Reports with up to **12 M long term data** for Temozolomide Capsules, 140 mg, and 180 mg located in Module 3.2.P.8

Based on the stability data generated to date, Barr is proposing to revise the expiration dating period for Temozolomide Capsules, 5 mg, and 20 mg.

(b) (4)

[redacted]

Enclosed in this amendment, please find the following supporting updated documentation.

3.2.P.8: Stability
- 3.2.P.8.1.1: Marketed Product Stability Protocol
- 3.2.P.8.1.4: Expiration Dating Period

Comment 2:
Labeling deficiencies were communicated to you via facsimile on May 8, 2008. You should address the issues in the May 8, 2008 communication prior to or concurrent with your response to this communication.

Response 2:
The labeling deficiencies stated in the Agency's Labeling Comments dated **April** 08, 2008 have been addressed by Barr via a Labeling Amendment on April 16, 2008.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (**version 2/5/09 rev. 7**). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

Lastly, please note that Barr Laboratories, Inc is an indirectly, wholly-owned subsidiary of Teva Pharmaceuticals, USA.

If you have any questions concerning this application, please contact Nicholas Tantillo at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director
Regulatory Affairs

barr Laboratories, Inc.

225 Summit Avenue, Montvale, NJ 07645 • 201-930-3300

February 9, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

PATENT CORRESPONDENCE

REFERENCE: **ANDA 78-879**
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, **5 mg, 20 mg, 100 mg and 250 mg** and the electronic Amendment to a pending Abbreviated New Drug Application dated March 21, 2008, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for two (2) additional strengths of Temozolomide Capsules, **140 mg and 180 mg.**

Reference is also made to the Patent Amendments dated June 28, 2007 and October 18, 2007 and Patent Correspondence dated February 3, 2009 in which Barr certified that the required notice letters were sent to the owners of U.S. Patent No. 5,260,291 which is the subject of the certification, and to the holder of the approved application under Section 505(b) of the Act by certified mail.

Reference is also made to the Amendment dated July 26, 2007 in which Barr notified the Agency that a litigation with respect to US Patent 5,260,291 has occurred for Temozolomide Capsules, **5 mg, 20 mg, 100 mg, and 250 mg.**

Litigation with respect to U.S. Patent No. 5,260,291 has also occurred within the 45-day period for Temozolomide Capsules, **140 mg and 180 mg.** On April 18, 2008, a formal complaint was filed by Schering Corporation and Cancer Research Technology Limited, against Barr, in the United States District Court of Delaware: Schering Corporation and Cancer Research Technology Limited v. Barr Laboratories, Inc., and Barr Pharmaceuticals, Inc. Civil Action No. 07-457-SLR to prevent Barr from proceeding with the commercialization of its product. This initiates the patent challenge process under the Hatch-Waxman Act. A copy of the complaint letter is provided in Module 1.3.5.

We will submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between Barr and the holder of the patent, or any other relevant information when it becomes available.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 2/8/09 rev.16). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

Please note that Barr Laboratories, Inc is an indirectly, wholly-owned subsidiary of Teva Pharmaceuticals, USA.

If you have any questions concerning this patent amendment, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Senior Director, Regulatory Affairs

TEVA PHARMACEUTICALS

Nicholas Tantillo
Senior Director, Regulatory Affairs

June 19, 2009

Electronic Submission

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773.

GRATUITOUS AMENDMENT

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to our Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg** strengths and the Amendment dated March 21, 2008 for the addition of the **140 mg and 180 mg strengths**.

At this time, Barr Laboratories, Inc. ('Barr') is submitting an amendment to provide updates to the pending application. The updates are listed below:

1. Demonstrate compliance with the requirements of the harmonized USP <61> and <62>, official May 1, 2009.
2. Removal of (b) (4) as alternate analytical testing sites.
3. Updated Excipients Specifications and Test Methods.
4. Added (b) (4) as an alternate vendor for Stearic Acid, NF (b) (4)
5. Updated Stability Reports for the 140 mg and 180 mg strengths.

1) Demonstrate compliance with the requirements of the harmonized USP <61> and <62>, official May 1, 2009.

In compliance with the revised USP <61> and <62> requirement, Barr is submitting the Microbial Examination testing information for each ingredient (drug substance and excipients) used in the formulation of Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, and the information is summarized in the table below:
Barr has performed the validation of Microbiological test analytical procedures to comply with the Microbial requirements to be effective in May 1, 2009.

Following this page, 3 pages withheld in full (b)(4)

400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677
Phone: 201.930.3650 Fax: 201.930.3318 Email: nicholas.tantillo@tevausa.com
www.tevausa.com

(b) (4)

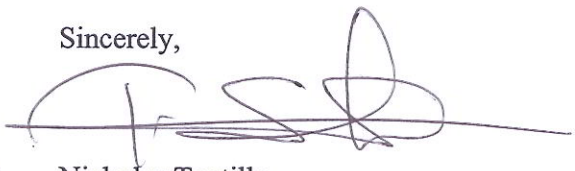
Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (**version 6/18/09 rev. 4**). Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

In accordance with 21 CFR Part 11.2(b) (2) and Docket 92S-0251 – Update Transmittal Memorandum 29, dated September 24, 2003, letters were forwarded to the New York and Baltimore District Offices certifying that the electronic CMC section was submitted to

CDER and that the ORA District Office can access electronic CMC submissions through the CDER Electronic Document Room.

If you have any questions concerning this application, please contact Nicholas Tantillo at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,



Nicholas Tantillo
Senior Director, Regulatory Affairs
Barr Laboratories, Inc., an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.

TEVA PHARMACEUTICALS

Nicholas Tantillo
Senior Director, Regulatory Affairs

August 20, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

REFERENCE: ANDA # 78-879
Temozolomide Capsules, 5mg, 20mg, 100mg, 140mg, 180mg and 250mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg and to the amendment dated March 21, 2008 for the addition of the 140 mg and 180 mg strengths of Temozolamide Capsules.

Reference is also made to a telephone conversation on August 20, 2009 between Joe Wetzel, OGD, and Nicholas Tantillo, Barr Laboratories Inc., in which the Agency requested that Barr submit a statement as soon as possible acknowledging that a Prior Approval Supplement will be submitted with complete supporting data to support the (b) (4).

As requested, Barr Laboratories, Inc. hereby acknowledges that a Prior Approval Supplement will be submitted with complete supporting data to support the (b) (4).

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 8/18/09 rev. 3). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

KR (for)

Nicholas Tantillo
Senior Director, Regulatory Affairs
Barr Laboratories, Inc.
an indirect, wholly-owned subsidiary of
Teva Pharmaceuticals USA

400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677
Phone: 201.930.3650 Fax: 201.930.3318 Email: nicholas.tantillo@tevausa.com
www.tevausa.com

Record of Telephone Conversation

Nicholas Tantillo of Barr Laboratories, Inc. was contacted and informed of the following:

Additional Information is Required:
A Signed Statement and commitment noting and acknowledging that a Prior Approval Supplement with complete and satisfactory supporting data will be required for any future reduction in [redacted] (b) (4)

Please Send via e-mail & FDA Gateway within 24 hours.

Date:
8/19/09

ANDA Number:
78-879

Product Name:
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg

Firm Name:
Barr Laboratories, Inc.

Firm Representative:
Nicholas Tantillo

Phone Number:
(201) 930-3650

FDA Contacts:
N.Patel:
240-276-8548

Ayesha:
240-276-8500

FDA Fax No:
240-276-8503

FDA Representative:
Signatures:

\\Cdsnas1\OGDS11\Chemistry Division I\Team 3\T-CONS\78879 Barr Tcon 082009 jrw.doc

Wetzel, Joseph

From: Richardson, Krista [Krista.Richardson@barrlabs.com]
Sent: Thursday, August 20, 2009 10:50 AM
To: Wetzel, Joseph
Cc: O'Dea, Linda; Tantillo, Nicholas
Subject: RE: Call Report - Temozolomide Capsules - ANDA 78-879
Attachments: 1.2 Cover letter.pdf

Dear Mr. Wetzel,
As requested in your telephone conversation with Nicholas Tantillo this morning, please find attached a statement from Barr acknowledging that a Prior Approval Supplement with complete supporting data will be submitted to support the (b) (4) for Temozolomide Capsules (ANDA 78-879).

This statement will be followed up with the standard electronic submission as well.

Kind Regards,

Krista Richardson
Manager, Regulatory Affairs
Barr Laboratories, Inc.
400 Chestnut Ridge Road
Woodcliff Lake, New Jersey 07677
Ph. 201-594-5212
Fax 201-930-3318

From: Tantillo, Nicholas
Sent: Thursday, August 20, 2009 9:58 AM
To: O'Dea, Linda; Noble Gray, Elisabeth; Richardson, Krista
Cc: Peer, Daniel
Subject: Call Report - Temozolomide Capsules - ANDA 78-879

We received a voicemail from OGD reviewer Joe Wetzel regarding Temozolomide Capsules. ANDA 78-879. He said that he wants us to submit a statement asap acknowledging that we will submit a PAS with complete supporting data to support the (b) (4) He asked that we e-mail it to him at joseph.wetzel@fda.hhs.gov and that we follow it up with the standard electronic submission. He wants this asap in order to keep the ANDA moving to TA.
Nick

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

/s/

JOSEPH R WETZEL

08/21/2009

TCon 8/19/09 Information Request
Approvable

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-879 Applicant Barr Laboratories, Inc.
Drug Temozolomide Capsules, 5, 20,100, 140, 180, and 250 mg Strength(s)_____

APPROVAL ☐ **TENTATIVE APPROVAL** ☒ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer**	Date 6 August 2009	Date_____
Chief, Reg. Support Branch	Initials MHS	Initials_____

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD =_____ NDA#_____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
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: Tentative Approval
Comments: ANDA submitted on 3/20/2007, BOS=Temodar NDA 21029, PIV to '291, Barr intends to 'carve-out' the ODE exclusivity. ANDA ack for filing with PIV for the 5 mg, 20 mg, 100 mg and 250 mg on 3/20/2007(LO dated 6/7/2007). On 7/2/2007 the sponsor submitted a patent amendment-RR from Schering Plough in Kenilworth NJ signed and dated 6/12/2007. 7/27/07 XP-on 7/20/2007 suit was filed against Barr in the D of DE for infringement of the '291 patent, the cover letter for the 7/20/07 submission indicates that the CA # is 07 CV 457. Also on 7/27/07, Ropes and Gray-counsel for Schering Plough also provided a copy of the lawsuit-this information is consistent with the information provided by Barr. 30 month stay of approval=12/12/2009. Sponsor submitted XP on 10/19/2007-notice was also provided to Cancer Research Technolog Ltd.-notice sent to Cancer Research… in Cambridge MA on 7/26/2007, RR signed and dated 7/31/2007, notice was also sent via FedEx on 7/26 with the FedEx notice being delivered on 7/30/2007.

On 3/24/2008 the sponsor submitted a NSA seeking approval of the 140 mg and 180 mg strengths, BOS= Temodar NDA 21029, PIV to '291, carving out the ODE. XP provided on 2/3/2009-RR from Schering Plough in Kenilworth NJ signed and dated 3/26/2008, RR from Cancer REsearch Tech signed and dated 3/28/2008, notice was also provided to both of these parties using FedEx with notice delivered on 3/25/2008. XP provided on 2/9/2009-the original CA 07-457 was amended on 4/18/2008 to include the 140 mg and 180 mg strengths. With respect to these strengths Barr was again sued on the '291 patent. Suit brought within 45 days so 30 month stay of approval=9/25/2010(the FedEx RRs were used to calculate the 30 month stay as the sponsor rec'd authorization to use FedEx from the AGency on 3/21/2008).

ANDA is eligible for TA only due to unexpired 30 month stays of approval:
30 month stay for 5 mg, 20 mg, 100 mg and 250 mg=12/12/2009
30 month stay for 140 mg and 180 mg=9/25/2010.
This ANDA is currently the only ANDA pending in OGD for these drug products. Since the sponsor submitted PIV certifications they are also eligible for 180 day exclusivity even though they currently block noone. In order to retain eligibility for exclusivity on the 5 mg, 20 mg, 100 mg and 250 mg strengths, tentative approval for this ANDA must be issued by NLT 9/20/2009.

2. Project Manager, Nitin Patel Team 3	Date_____	Date_____
Review Support Branch	Initials se	Initials_____

Original Rec'd date 3/21/08
Date Acceptable for Filing_____
Patent Certification (type) IV
Date Patent/Exclus.expires 2/11/2014
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 11/15/07
Date of Office Bio Review 7/6/09
Date of Labeling Approv. Sum 5/8/08
Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒

Priority Approval Yes ☐ No ☒ Modified-release dosage form: Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes ☐
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer: Labeling Team Leader:
Date8/19/2009 Date8/19/2009
Name/InitialsAP Name/InitialsJG

Comments:

From: Grace, John F
Sent: Wednesday, August 19, 2009 9:42 AM
To: Payne, Angela; Patel, Nitin K. (CDER/OGD)
Subject: RE: Request for labeling endorsement; ANDA 78-879; Temozolomide Capsules; Barr

concur

From: Payne, Angela
Sent: Tuesday, August 18, 2009 7:00 PM
To: Patel, Nitin K. (CDER/OGD); Grace, John F
Subject: RE: Request for labeling endorsement; ANDA 78-879; Temozolomide Capsules; Barr

John/Nitin,

The labeling approval summary signed 5/9/2008 remains acceptable. There are no new approved changes to the RLD labels or labeling in DARRTS,OB, or USP. There are (b) (4) supplements for the RLD. Should a supplement gain approval status prior to the generic being fully approved, then the generic labeling will have to revised.

The approval letter appears to missing some amendment dates? I think the Feb. 12, 2008, March 21, 2008 and April 16, 2008 may also have to be listed in the letter. The dates corresponds to the labeling pieces.

Angela

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 8/17/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsSL
Comments:Revised version saved in the V drive.

5. Div. Dir./Deputy Dir. Date8/22/09
Chemistry Div. I InitialsPS

Comments:CMC acceptable for all strengths

6. Frank Holcombe **First Generics Only** Date9/9/09
Assoc. Dir. For Chemistry InitialsRR
Comments: (First generic drug review)
CMC acceptable; for Frank,

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date 9/10/2009
Director, DLPS Initials wpr

Para.IV Patent Cert: Yes☒ No☐;Pending Legal Action: Yes ☒ No ☐; Petition: Yes☐ No☒
Comments: BOS=Temodar NDA 21029, applicant made a PIV to '291; the applicant intends to carve-out the ODE exclusivity. The applicant submitted on 7/2/2007 a patent amendment-RR from Schering Plough in Kenilworth NJ signed and dated 6/12/2007. On 7/20/2007 suit was filed against the applicant in the D of DE for infringement of the '291 patent. 30 month stay of approval=12/12/2009. On 3/24/2008 the applicant submitted a NSA seeking approval of the 140 mg and 180 mg strengths, applicant made a PIV to '291, carving out the ODE. The applicant was sued again on the '291 patent. Suit brought within 45 days so 30 month stay of approval=9/25/2010.
ANDA is eligible for TA only due to unexpired 30 month stays of approval:
30 month stay for 5 mg, 20 mg, 100 mg and 250 mg=12/12/2009, 30 month stay for 140 mg and 180 mg=9/25/2010. Labeling acceptable 5/8/2008 per TA Summary and endorsed by TL on 8/19/2009 (no updates to RLD labeling); Bio acceptable 7/6/2009 (waivers granted per BCS); EER acceptable 11/15/2007.

This ANDA is currently the only ANDA pending in OGD for these drug products. Since the applicant submitted PIV certifications they are also eligible for 180 day exclusivity (plus there are no other applications to be blocked).

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, SELECT PM NAME Team TEAM # Date _____

Review Support Branch Initials _____
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
_____Time notified of approval by phone
_____Time approval letter faxed

FDA Notification:
_____Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

THOMAS O HINCHLIFFE
09/10/2009

NITIN K PATEL
09/11/2009

ROPES & GRAY LLP
1211 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-8704
WWW.ROPESGRAY.COM

Denise L. Loring
212-596-9069
Denise.Loring@ropesgray.com

December 22, 2009

orig - 1
SD - 30

VIA FACSIMILE AND FEDEX

Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 4
7519 Standish Place
Rockville, MD 20855

Re: ANDA No. 78-879
Temozolomide Capsules,
5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Dear Sir or Madam:

This letter is further to my previous letters of July 26, 2007 and September 7, 2007, which were sent to you pursuant to Section 314.107(f)(2) of the regulations.

My previous letters notified you that on July 20, 2007, Cancer Research Technology Limited and Schering Corporation filed an action for infringement of U.S. Patent 5,260,291 ("the '291 patent") against Barr Laboratories, Inc., the holder of the above-referenced ANDA application. The '291 patent is listed in the Orange Book for TEMODAR® (temozolomide) Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg. Copies of my July 26 and September 7 letters are attached at Tabs A and B.

I write to advise you of certain changes in the identities of the parties-in-interest in this case. In July 2008, Barr and Teva Pharmaceutical Industries Ltd. ("Teva") announced that Teva would acquire Barr; the merger was completed in December 2008. Separately, and effective November 3, 2009, Schering-Plough Corporation, the corporate parent of the NDA holder, Schering Corporation, merged with Merck & Co., Inc. The new entity is known as Merck & Co., Inc. ("Merck").

A bench trial was held in this matter from March 30, 2009 to April 2, 2009 in the United States District Court for the District of Delaware. A decision is pending.

Finally, I wish to respectfully remind you, in view of my previous correspondence, that under Section 505(j)(5)(B)(iii) of the Act and Section 314.107(b)(3) of the regulations, the above-referenced ANDA may not be made effective until January 27, 2010 (*i.e.*, 30 months from July 27, 2007, the date by which both the patent holder Cancer Research Technology Limited and the NDA holder Schering Corporation received notice of Barr Laboratories' ANDA), unless the Court extends or reduces this period.

Respectfully submitted,

Denise L. Loring

TEVA PHARMACEUTICALS

Nicholas Tantillo
Senior Director, Regulatory Affairs

January 29, 2010

Electronic Submission

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773.

MINOR AMENDMENT- FINAL APPROVAL REQUESTED

REFERENCE: ANDA 78-879
Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg

Reference is made to our Abbreviated New Drug Application dated March 19, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg, and 250 mg strengths and the Amendment dated March 21, 2008 for the addition of the 140 mg and 180 mg strengths.

Reference is also made to the Agency's tentative approval letter dated September 11, 2009 in which the Agency noted that Barr should submit a "Minor Amendment – Final Approval Requested" in order to reactivate this application. The Agency also requested that this amendment provide the legal/regulatory basis for our request for final approval.

At this time, Barr Laboratories, Inc. ('Barr') is requesting final approval for ANDA 78-879.

Basis for Requesting Final Approval

The ANDA contains a paragraph IV patent certification with respect to the listed U.S. Patent No. 5,260,291 (the '291 patent) under section 505(j)(2)(A)(vii)(IV) of the Act, stating that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Temozolomide Capsules, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg under this application.

400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677
Phone: 201.930.3650 Fax: 201.930.3318 Email: nicholas.tantillo@tevausa.com
www.tevausa.com

Litigation with respect to the '291 patent was brought against Barr within the statutory 45-day period in the United States District Court for the District of Delaware [Cancer Research Technology Limited and Schering Corporation v. Barr Laboratories, Inc., Civil Action No. 07-cv-00457].

On January 26, 2010 the court decided that the '291 patent was unenforceable due to prosecution laches and/or inequitable conduct. Therefore, final approval can now be granted.

Enclosed is a copy of the court order and decision.

We request that approval of ANDA 78-879 be made effective immediately.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Trend Micro™ OfficeScan™ Client version 8.0. Barr Laboratories, Inc. also declares that all original signed paper certifications have been provided in the original paper format.

If you have any questions concerning this application, please contact Nicholas Tantillo at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

KR (for)

Nicholas Tantillo
Senior Director, Regulatory Affairs
Barr Laboratories, Inc., an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.

cc: Robert West, Deputy Director, OGD
Martin Shimer, Branch Chief, DLPS, OGD

TEVA PHARMACEUTICALS

Nicholas Tantillo
Senior Director, Regulatory Affairs

February 19, 2010

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

REFERENCE: **ANDA # 78-879**
Temozolomide Capsules, 5mg, 20mg, 100mg, 140mg, 180mg and 250mg

Reference is made to Barr Laboratories Inc., ('Barr') electronic Abbreviated New Drug Application dated March 19, 2007, submitted under section 505(j) of the Federal Food, Drug and Cosmetic Act for Temozolomide Capsules, 5 mg, 20 mg, 100 mg and 250 mg and to the amendment dated March 21, 2008 for the addition of the 140 mg and 180 mg strengths of Temozolamide Capsules.

Reference is also made to Barr's Request for Final Approval dated January 29, 2010, and the telephone conversation on February 19, 2010 between Tran Trang, Project Manager, OGD, and Nicholas Tantillo, Barr Laboratories Inc., in which the Agency requested that Barr submit a statement that no changes have been made since Barr received Tentative Approval on September 10, 2009.

As requested, Barr Laboratories, Inc. hereby acknowledges that no changes have been made in the conditions under which the ANDA was Tentatively Approved.

Barr Laboratories, Inc. declares that the electronic information contained in the enclosed CD-ROM is **virus-free** and was checked by using Symantec's AntiVirus Corporate Edition Software (version 8/18/09 rev. 3). Barr Laboratories, Inc. also declares that all original signed documents have been provided in the original paper format.

If you have any questions, please contact me by phone at (201) 930-3650 or by fax at (201) 930-3318.

Sincerely,

KR (for)

Nicholas Tantillo
Senior Director, Regulatory Affairs
Barr Laboratories, Inc.
an indirect, wholly-owned subsidiary of
Teva Pharmaceuticals USA

400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677
Phone: 201.930.3650 Fax: 201.930.3318 Email: nicholas.tantillo@tevausa.com
www.tevausa.com

From: CDER EESQUESTIONS
Sent: Friday, February 26, 2010 9:02 AM
To: West, Robert L
Cc: Ames, Timothy W; Rickman, William P; Tran, Trang; Shimer, Martin; Buehler, Gary J
Subject: RE: BARR'S ANDA 78-879 FOR TEMOZOLOMIDE CAPSULES - FIRST GENERIC APPROVAL - OAI ALERT FOR BARR LABORATORIES?

Hi Bob,

I believe the Barr compliance issues pertain particularly to (b) (4) products, however please resubmit the EER so that the district can make an updated compliance recommendation for this application.

Sincerely,

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: West, Robert L
Sent: Thursday, February 25, 2010 7:54 AM
To: CDER EESQUESTIONS
Cc: Ames, Timothy W; Rickman, William P; Tran, Trang; Shimer, Martin; Buehler, Gary J
Subject: BARR'S ANDA 78-879 FOR TEMOZOLOMIDE CAPSULES - FIRST GENERIC APPROVAL - OAI ALERT FOR BARR LABORATORIES?
Importance: High

Dear EES:

Barr's ANDA 78-879 for Temozolomide Capsules (Temodar/Schering) was granted tentative approval on September 10, 2009. Final approval was blocked at that time by ongoing patent litigation between Barr and Schering/Merck.

Barr prevailed in the patent litigation with the court finding that the listed patent is unenforceable. As a result, Barr has requested final approval of this ANDA.

I currently have the approval package for this first-generic ANDA and it is otherwise ready for approval. However, a check of EES reveals a potential OAI Alert for Barr's manufacturing, packaging, labeling site in (b) (4). I cannot find any comments in EES pertaining to this action. Is this a real "OAI" Alert and are there grounds to withhold approval of this application?

Thank you,

Bob

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78879	ORIG-1	BARR LABORATORIES INC	TEMOZOLOMIDE

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

/s/

TRANG Q TRAN
03/01/2010

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-879 Applicant Barr Laboratories, Inc.
Drug Temozolomide Capsules, 5, 20,100, 140, 180, and 250 mg Strength(s)_____

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer**	Date 6 August 2009	Date 2/25/10
Chief, Reg. Support Branch	Initials MHS	Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = Temodar NDA# 21-029
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
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: Tentative Approval
Comments: ANDA submitted on 3/20/2007, BOS=Temodar NDA 21029, PIV to '291, Barr intends to 'carve-out' the ODE exclusivity. ANDA ack for filing with PIV for the 5 mg, 20 mg, 100 mg and 250 mg on 3/20/2007(LO dated 6/7/2007). On 7/2/2007 the sponsor submitted a patent amendment-RR from Schering Plough in Kenilworth NJ signed and dated 6/12/2007. 7/27/07 XP-on 7/20/2007 suit was filed against Barr in the D of DE for infringement of the '291 patent, the cover letter for the 7/20/07 submission indicates that the CA # is 07 CV 457. Also on 7/27/07, Ropes and Gray-counsel for Schering Plough also provided a copy of the lawsuit-this information is consistent with the information provided by Barr. 30 month stay of approval=12/12/2009. Sponsor submitted XP on 10/19/2007-notice was also provided to Cancer Research Technolog Ltd.-notice sent to Cancer Research… in Cambridge MA on 7/26/2007, RR signed and dated 7/31/2007, notice was also sent via FedEx on 7/26 with the FedEx notice being delivered on 7/30/2007.

On 3/24/2008 the sponsor submitted a NSA seeking approval of the 140 mg and 180 mg strengths, BOS= Temodar NDA 21029, PIV to '291, carving out the ODE. XP provided on 2/3/2009-RR from Schering Plough in Kenilworth NJ signed and dated 3/26/2008, RR from Cancer REsearch Tech signed and dated 3/28/2008, notice was also provided to both of these parties using FedEx with notice delivered on 3/25/2008. XP provided on 2/9/2009-the original CA 07-457 was amended on 4/18/2008 to include the 140 mg and 180 mg strengths. With respect to these strengths Barr was again sued on the '291 patent. Suit brought within 45 days so 30 month stay of approval=9/25/2010(the FedEx RRs were used to calculate the 30 month stay as the sponsor rec'd authorization to use FedEx from the AGency on 3/21/2008).

ANDA is eligible for TA only due to unexpired 30 month stays of approval:
30 month stay for 5 mg, 20 mg, 100 mg and 250 mg=12/12/2009
30 month stay for 140 mg and 180 mg=9/25/2010.
This ANDA is currently the only ANDA pending in OGD for these drug products. Since the sponsor submitted PIV certifications they are also eligible for 180 day exclusivity even though they currently block noone. In order to retain eligibility for exclusivity on the 5 mg, 20 mg, 100 mg and 250 mg strengths, tentative approval for this ANDA must be issued by NLT 9/20/2009.

Update 2/16/2010-On January 25, 2010 the D of DE ruled in favor of Barr laboratories and determined that the '291 patent was unenforceable due to inequitable conduct. This decision effectively ends the 30 month stay of approval for all strengths of this ANDA. This ANDA is eligible for immediate Full Approval with an award of 180 day exclusivity.

2. **Project Manager**, Nitin Patel Team 3	Date_____	Date 3/1/10
Review Support Branch	Initials se	Initials TT

Original Rec'd date 3/19/07
Date Acceptable for Filing 3/20/07
Patent Certification (type) IV
Date Patent/Exclus.expires 2/11/2014

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 11/15/07
Date of Office Bio Review 7/6/09
Date of Labeling Approv. Sum 5/28/08

Citizens' Petition/Legal Case Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

3. Labeling Endorsement

Reviewer:
Date8/19/09;2/18/10
Name/InitialsAP

Labeling Team Leader:
Date8/19/09;2/18/10
Name/InitialsJG

Comments:

___From: Grace, John F
Sent: Thursday, February 18, 2010 10:02 AM
To: Tran, Trang
Cc: Payne, Angela
Subject: RE: ANDA-078879 Product Name: TEMOZOLOMIDE Dosage Form: CAPSULE Applicant: BARR LABORATORIES INC

concur.
Sorry,
I wasn't cc'd on angela's concurrence.

_____
From: Tran, Trang
Sent: Thursday, February 18, 2010 9:56 AM
To: Grace, John F
Subject: FW: ANDA-078879 Product Name: TEMOZOLOMIDE Dosage Form: CAPSULE Applicant: BARR LABORATORIES INC

Hi John,

Can you have your labeling concurrence for this application?

Thanks,

Trang

_____
From: Payne, Angela
Sent: Thursday, February 18, 2010 8:11 AM
To: Tran, Trang; West, Robert L
Subject: RE: ANDA-078879 Product Name: TEMOZOLOMIDE Dosage Form: CAPSULE Applicant: BARR LABORATORIES INC

Tran,

This one remains acceptable for labeling with the labeling AP that we have. At this time there is no updated labeling needed.

Angela_____
From: Grace, John F
Sent: Wednesday, August 19, 2009 9:42 AM
To: Payne, Angela; Patel, Nitin K. (CDER/OGD)
Subject: RE: Request for labeling endorsement; ANDA 78-879; Temozolomide Capsules; Barr

concur

_____
From: Payne, Angela

Sent: Tuesday, August 18, 2009 7:00 PM
To: Patel, Nitin K. (CDER/OGD); Grace, John F
Subject: RE: Request for labeling endorsement; ANDA 78-879; Temozolomide Capsules; Barr

John/Nitin,

The labeling approval summary signed 5/9/2008 remains acceptable. There are no n approved changes to the RLD labels or labeling in DARRTS,OB, or USP. There are (b) (4) supplements for the RLD. Should a supplement gain approval status prior to the generic being fully approved, then the generic labeling will have to revised.

The approval letter appears to missing some amendment dates? I think the Feb. 12, 2008, March 21, 2008 and April 16, 2008 may also have to be listed in the letter. The dates corresponds to the labeling pieces.

Angela

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 8/17/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials SL
Comments:Revised version saved in the V drive.

18Feb10: DTR - AP chans to approval letter saved to V drive.

5. Div. Dir./Deputy Dir. Date 8/22/09
Chemistry Div. I Initials PS

Comments:CMC acceptable for all strengths
No changes from TA to AP-still ok, PS 2/24/10

6. Frank Holcombe **First Generics Only** Date 9/9/09
Assoc. Dir. For Chemistry Initials RR
Comments: (First generic drug review)
CMC acceptable; for Frank,

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Temodar Capsules 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg
Schering corp. NDA 21-029

8. Peter Rickman Date 9/10/2009
Director, DLPS Initials wpr
Para.IV Patent Cert: Yes☒ No☐;Pending Legal Action: Yes ☒ No ☐; Petition: Yes☐ No☒
Comments: BOS=Temodar NDA 21029, applicant made a PIV to '291; the applicant intends to carve-out the ODE exclusivity. The applicant submitted on 7/2/2007 a patent amendment-RR from Schering Plough in Kenilworth NJ signed and dated 6/12/2007. On 7/20/2007 suit was filed against the applicant in the D of DE for infringement of the '291 patent. 30 month stay of approval=12/12/2009. On 3/24/2008 the applicant submitted a NSA seeking approval of the 140 mg and 180 mg strengths, applicant made a PIV to '291, carving out the ODE. The applicant was sued again on the '291 patent. Suit brought within 45 days so 30 month stay of approval=9/25/2010. ANDA is eligible for TA only due to unexpired 30 month stays of approval: 30 month stay for 5 mg, 20 mg, 100 mg and 250 mg=12/12/2009, 30 month stay for 140 mg and 180 mg=9/25/2010. Labeling acceptable 5/8/2008 per TA Summary and endorsed by TL on 8/19/2009 (no updates to RLD labeling); Bio acceptable 7/6/2009 (waivers granted per BCS); EER acceptable 11/15/2007.

This ANDA is currently the only ANDA pending in OGD for these drug products. Since the applicant submitted PIV certifications they are also eligible for 180 day exclusivity (plus there are no other applications to be blocked).

OR

8. Robert L. West Date 3/1/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Refer to the regulatory/legal review presented above by M.Shimer for basis of approval of this ANDA.

Barr is eligible for 180-day generic drug exclusivity for this drug product.

Barr has "carved-out" information pertaining to the Orphan Drug Exclusivity - "Treatment of adult patients with newly diagnosed glioblastoma multiforme . . . " This is acceptable. final-printed labeling remains acceptable for approval 2/18/10.

CMC remains acceptable for final approval - Regulatory Assessment dated 2/24/10.

Final-printed lableing (FPL) remains acceptable for approval. Barr has elected to "carve-out" information pertaining to the Orphan Drug Exclusivity (Treatment of adult patients with newly diagnosed glioblastoma multiforme . . . ". This is acceptable.

Acceptable EES dated 11/15/07 (Verified 3/1/10). At present, there appears to be an "OAI" Alert associated with the Barr manufacturing site for this drug product. However, the "OAI" Alert does not apply to this ANDA according to a communication received from OC and filed in DARRTS. There are no "OAI" Alerts accociated with this ANDA.

This ANDA is recommended for final approval.

9. Gary Buehler Date 3/1/10
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Nitin Patel Team 3 Date3/1/10

Review Support Branch Initials _____
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3/1/10Time notified of approval by phone
3/1/10Time approval letter faxed

FDA Notification:
3/1/10Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 021029 Product 004 in the OB_Rx list.

<>

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021029	004	5260291	Aug 11, 2013	Y	Y	U - 619	
N021029	004	5260291*PED	Feb 11, 2014				

<>

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021029	004	ODE	Mar 15, 2012

Additional information:

1. **Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).**
2. **Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.**

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78879	ORIG-1	BARR LABORATORIES INC	TEMOZOLOMIDE

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/s/

TRANG Q TRAN
03/01/2010