CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-277

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-277 SUPPL # HFD # 150

Trade Name Temodar

Generic Name temozolomide

Applicant Name Schering

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The required study, P02467, is a bioequievalence study because it compared the exposure of of temozolomide and its active metabolite, MTIC after a 1.5 hour IV infusion of temozolomide to that after the oral capsules.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21029 Temodar tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Paul Zimmerman
Title: Project Manager
Date: 11-14-08

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Robert Justice

11/24/2008 11:09:50 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-277 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DDOP PDUFA Goal Date: 11-24-08 Stamp Date: 1/23/2008

Proprietary Name: Temodar

Established/Generic Name: temozolomide

Dosage Form: for Injection

Applicant/Sponsor: Schering

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: refractory anaplastic astrocytoma

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-277 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DDOP PDUFA Goal Date: 11-24-08 Stamp Date: 1/23/2008

Proprietary Name: Temodar

Established/Generic Name: temozolomide

Dosage Form: for Injection

Applicant/Sponsor: Schering

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: refractory anaplastic astrocytoma

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

Q1: Does this indication have orphan designation?

- ☒ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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/s/

Paul Zimmerman

11/3/2008 04:42:43 PM

Zimmerman, Paul F

From: Ceruzzi, Marion [marion.ceruzzi@spcorp.com]
Sent: Monday, November 24, 2008 9:37 AM
To: Zimmerman, Paul F
Subject: RE: NDA 22-277 -PPI & PI

Hi Paul,

We are in agreement for the text for the PI and PPI.

Regards,

Marion

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Monday, November 24, 2008 8:29 AM
To: Ceruzzi, Marion
Subject: RE: NDA 22-277 -PPI

thanks

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Monday, November 24, 2008 8:29 AM
To: Zimmerman, Paul F
Subject: RE: NDA 22-277 -PPI

Hi,

Received these changes as well as the PI. We are reviewing them and will get back to you as soon as possible.

Regards,

Marion

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Monday, November 24, 2008 8:23 AM
To: Ceruzzi, Marion
Subject: NDA 22-277 -PPI

Dear Marion,

Please let me know if to agree with these revisions and with version of the PPI.

Paul

<<Temodar PPI 11-20-08 for submission from firm 11-20-08 plus RJ edit 11-24-08.doc>>

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/s/

Paul Zimmerman

11/25/2008 09:16:13 AM

CSO

From: Zimmerman, Paul F
To: "Karjian, Lucine";
cc: "Ceruzzi, Marion";
Subject: RE: NDA 22-277 for Temodar - Action letter
Date: Tuesday, November 25, 2008 12:23:41 PM

Lucine,

You should contact Compliance regarding this.

Paul

From: Karjian, Lucine [mailto:lucine.karjian@spcorp.com]
Sent: Tuesday, November 25, 2008 10:50 AM
To: Karjian, Lucine; Zimmerman, Paul F
Cc: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar - Action letter

Dear Paul,

This is a follow up to our phone discussion a few minutes ago. Back in May/June 2008, I received e-mail and phone communications from Captain Sharon Thoma of the FDA. Below is a summary of our communications:

- I clarified to Capt. Thoma that temo (active and finished product) are not stored, manufactured, packaged or tested at Brinny.
- Brinny is responsible only for paper-release of active temozolomide.
- Capt. Thoma suspected that perhaps site information was entered into FDA computer systems incorrectly. She said to me that she was not sure why she would inspect Brinny for NDA 22-277.
- She asked for the CMC section of the NDA, which I sent to her in its entirety.
- Her verbal feedback at the end of the inspection related to paper-release activities at Brinny was positive.

Please let me know if you need any clarification regarding the above.
Regards.
Lucine

-----Original Message-----

From: Karjian, Lucine
Sent: Tuesday, November 25, 2008 10:19 AM
To: 'Zimmerman, Paul F'
Cc: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar - Action letter

Dear Paul,
During the inspection of the Brinny site, Captain Sharon Thoma (FDA), who conducted the inspection, did not have any observations related to this NDA (22-277). Any operations at this site related to temo IV are limited to paper-release of the active temozolomide. No other operations (manufacturing or testing) take place at this site. From verbal communications, Captain Thoma was pleased with the level of control that exists at Brinny as related to paper-release of temozolomide active ingredient.

Would it be possible to check with the Compliance Division to obtain clarification regarding this issue?
Thank you and regards.
Lucine

> -----Original Message-----
> **From:** Ceruzzi, Marion
> **Sent:** Tuesday, November 25, 2008 10:06 AM
> **To:** 'Zimmerman, Paul F'
> **Cc:** Karjian, Lucine
> **Subject:** RE: NDA 22-277 for Temodar - Action letter
> **Importance:** High
>
> Dear Paul,
>
> I received your email. Please call me at your as soon as you can we have an answer for you regarding the Brinny Plant.
>
> With regards to the toxicology study, I had thought we agreed with the timelines of protocol submission in Jan. first animal initiated in March and final report at the end of December.
>
> The second bullet point of the letter indicates we can just file the final tox report.

Please let us know if:

1. the timelines are still applicable
2. all you need is the final report in Dec 2009

Thanks and Regards,

Marion

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Tuesday, November 25, 2008 8:23 AM
To: Ceruzzi, Marion
Subject: NDA 22-277 for Temodar - Action letter

Dear Marion,

Attached please find a copy of the action letter for NDA 22-277. Please let me know when you receive this email. The letter is being mailed to you. Please call me if you have questions.

Thanks,
Paul
<<CR LETTER 11-24-08 w PI-PIS-PPI signed-p1.pdf>>

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/s/

Paul Zimmerman

11/25/2008 02:38:14 PM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, November 21, 2008 8:28 AM
To: 'Ceruzzi, Marion'
Subject: RE: NDA 22-277 for Temodar- postmarketing

Marion,

That is acceptable.

Thanks,
Paul

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Thursday, November 20, 2008 4:32 PM
To: Zimmerman, Paul F
Subject: RE: NDA 22-277 for Temodar- postmarketing

Hi,

I just spoke with our Toxicology dept. because of varying animal arrival dates, condition of animals we cannot confirm that far out to an exact date. Although we are committed to start the week of March 2, we cannot guarantee for the reasons above the exact date.

Our Tox. lead therefore suggested rather than state March 2, that we state March 9.

Is that acceptable for study start date?

Thanks and Regards,

Marion

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Thursday, November 20, 2008 4:18 PM
To: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar- postmarketing

Marion,

We have been advised that we need to have specific dates for this. Is the following acceptable?

Final protocol Submission:	January 9, 2009
Study Start Date:	March 2, 2009
Final Report Submission:	December 31, 2009

Paul

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Monday, November 10, 2008 2:33 PM

To: Zimmerman, Paul F
Cc: Karjian, Lucine
Subject: RE: NDA 22-277 for Temodar- postmarketing

Dear Paul,

Lucine and I just had a discussion with the team regarding the delivery of tox supplies and activities surrounding the production of the tox report per the Division's request.

I will send a formal cover letter with these dates (as listed below) to the NDA as a Post-Marketing Commitment when I hear back from you that this is acceptable to the Division.

Per the November 4, 2008 email communication received from Mr.. Zimmerman of your Division, the Sponsor commits to a post-marketing rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4) that mimics a single cycle of the approved clinical schedule (daily x 5 every 28 days). The study will utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

The timelines for this study are listed below:

Final Protocol Submission by: January 9, 2009
Study Start: by approximately March 2, 2009
Final Report Submission by : December 31, 2009

Regards,

Marion

-----Original Message-----
From: Karjian, Lucine
Sent: Friday, November 07, 2008 2:04 PM
To: 'Zimmerman, Paul F'
Cc: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar- postmarketing

Dear Paul,

Thank you very much for this very critical clarification. We intend to provide you with the requested dates by Monday, Nov. 10, or the latest by Tuesday morning, Nov 11. At this time, we are refining the delivery date of the tox supplies to our research facility so that we can forecast an accurate date for the initiation of the tox study. I will continue to keep you posted on our progress, but I'd like to assure you that we are very close to projecting reliable timelines.

Please let me know if you have any other questions.
Thank you and regards.
Lucine

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Friday, November 07, 2008 12:46 PM
To: Karjian, Lucine
Cc: Ceruzzi, Marion

Subject: RE: NDA 22-277 for Temodar- postmarketing

We intend that the protocol review will be "FYI."
Paul

From: Karjian, Lucine [mailto:lucine.karjian@spcorp.com]
Sent: Thursday, November 06, 2008 2:53 PM
To: Zimmerman, Paul F
Cc: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar- postmarketing

Dear Paul,
The toxicology protocol will reflect the study elements and comments provided in your e-mail below. FDA has requested the date for final protocol submission. For clarification, does the FDA intend to review the protocol prior to execution as 'FYI' or to provide input?

Can you kindly clarify so that we may determine the remaining dates for study start and final report submission.
Thank you and regards.
Lucine

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]

Sent: Thursday, November 06, 2008 9:04 AM
To: Karjian, Lucine; Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar- postmarketing

Thanks

From: Karjian, Lucine [mailto:lucine.karjian@spcorp.com]
Sent: Thursday, November 06, 2008 8:49 AM
To: Zimmerman, Paul F; Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar- postmarketing

Dear Paul,
Our team is having multiple discussions regarding delivery of spiked API to toxicology so that they can create timelines to initiate the study. I expect to get additional details later today and will share with you as soon as I have it. I will send you an e-mail at the end of today to update you on our progress.
Thank you.
Regards.
Lucine

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Thursday, November 06, 2008 8:16 AM
To: Ceruzzi, Marion; Karjian, Lucine
Subject: RE: NDA 22-277 for Temodar- postmarketing

Lucine,
Can you estimate when you will propose the dates?
Paul

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Tuesday, November 04, 2008 12:26 PM
To: Zimmerman, Paul F; Karjian, Lucine
Subject: RE: NDA 22-277 for Temodar-postmarketing

Thanks very much Paul. I have passed this on to our Toxicology colleagues and either Lucine or I will get back to you with the information you requested.

Regards,

Marion

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]

Sent: Tuesday, November 04, 2008 12:10 PM
To: Ceruzzi, Marion; Karjian, Lucine
Subject: NDA 22-277 for Temodar-postmarketing

Dear Marion,

The clinical and nonclinical studies submitted with this NDA do not directly test intravenous exposures of (b) (4) impurities, (b) (4) at levels that are comparable to the proposed clinical formulation. The submitted oral toxicity study in rats of temozolomide spiked with enhanced levels of (b) (4) (Study No.03451), relies on the unknown bioavailability of (b) (4) administered by this route and therefore does not fully qualify the current specifications for (b) (4) proposed for drug substance and drug product, respectively. These impurities may be associated with clinically significant toxicities

when administered intravenously. The following postmarketing study could address these concerns.

1. Perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4) This study should mimic a single cycle of the approved clinical schedule (daily x 5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4), respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

Final Protocol Submission:
by MM/DD/YY
Study Start:
by MM/DD/YY
Final Report Submission:
by MM/DD/YY

Please propose milestone dates.
Thanks
Paul

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/s/

Paul Zimmerman

11/21/2008 08:33:54 AM

CSO

Subject: Temodar-Package insert

Marion,

We have reviewed the 11-12-08 Package insert and we are in agreement the changes.

The file marked "clean" is the version that would be considered agreed upon and used for labeling. Please let me know if you agree with this version.

Paul

the tracked version is also attached as fyi

<<Temodar-PI-agreed upon- tracked version.doc>> <<Temodar-PI-agreed upon- CLEAN version.doc>>

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, November 04, 2008 12:10 PM
To: 'Ceruzzi, Marion'; 'Karjian, Lucine'
Subject: NDA 22-277 for Temodar- postmarketing

Dear Marion,

The clinical and nonclinical studies submitted with this NDA do not directly test intravenous exposures of (b) (4) impurities, (b) (4) at levels that are comparable to the proposed clinical formulation. The submitted oral toxicity study in rats of temozolomide spiked with enhanced levels of (b) (4) (Study No.03451), relies on the unknown bioavailability of (b) (4) administered by this route and therefore does not fully qualify the current specifications for (b) (4) proposed for drug substance and drug product, respectively. These impurities may be associated with clinically significant toxicities when administered intravenously. The following postmarketing study could address these concerns.

1. Perform a rodent bridging study comparing the toxicity of temozolomide alone with temozolomide spiked with (b) (4). This study should mimic a single cycle of the approved clinical schedule (daily x 5 every 28 days) and utilize concentrations of (b) (4) which exceed (b) (4) respectively, to adequately qualify these impurities at levels proposed in the current specifications for drug substance and drug product.

Final Protocol Submission:	by MM/DD/YY
Study Start:	by MM/DD/YY
Final Report Submission:	by MM/DD/YY

Please propose milestone dates.

Thanks

Paul

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/s/

Paul Zimmerman

11/4/2008 12:18:46 PM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, October 30, 2008 5:44 PM
To: 'Ceruzzi, Marion'
Subject: NDA 22-277 for Temodar

Dear Marion,

We have the following comments concerning the container, and carton, and all labeling. (We will most likely have additional comments about the package insert.)
Please revise the container, and carton and provide the revised the container, and carton by email and submission to the NDA.

Thanks
Paul

All Labels and Labeling

Delete the word (b) (4) from the dosage form statement so that it reads "(temozolomide) for injection".

The amount of each inactive ingredient should be included in the product DESCRIPTION section of PI, PPI, Carton Label and Vial Label. (In other words where ever the excipients appear).

Container Label

1. Relocate the product strength so that it appears directly beneath the established name and dosage form "(temozolomide) for injection".
2. Increase the prominence of the established name. The established name should have prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors including typography, layout, contrast, and other printing features. Please also ensure that it is ½ the size of the proprietary name. Additionally, use a heavier, darker font for the established name that provides better contrast against the shaded background.
3. Add a "Single use; discard after use" statement to the label.
4. All articles should display the expiration date. The expiration date should be displayed in high contrast to the background. The product expiration dating needs be included on the label of the vial and the carton.
5. To avoid administration errors, please consider adding "This product does not require additional dilution after reconstitution" to the Usual Dosage statement following the directions for reconstitution.

Carton Labeling

1. Delete the vial outline graphic on the principal display panel. It distracts from other important drug information.
2. Increase the prominence of the established name. The established name should have prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors including typography, layout, contrast, and other printing features. Please also ensure that it is ½ the size of the proprietary name. Additionally, use a heavier, darker font for the established name that provides better contrast against the shaded background.
3. Add a "Single use; discard after use" statement to the carton labeling.
4. All articles should display the expiration date. The expiration date should be displayed in high contrast to the background. The product expiration dating needs be included on the label of the vial and the carton.
5. To avoid administration errors, please consider adding "This product does not require additional dilution after reconstitution" to the Usual Dosage statement following the directions for reconstitution.

Thanks
Paul

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/s/

Paul Zimmerman

10/30/2008 05:51:48 PM

CSO

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Preliminary Internal Consult

Date: October 15, 2008

To: **Paul Zimmerman**
Regulatory Project Manager
DDOP

From: Stephanie Victor, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Subject: NDA 22-277
DDMAC PPI labeling comments for Temodar (temozolomide)

DDMAC appreciates the opportunity to provide comments. We have reviewed the proposed PPI for Temodar and offer the following comments:

Under the header, "**What are the possible or reasonably likely side effects of TEMODAR?"** (emphasis original) the PPI lists the most common side effects (nausea and vomiting) before discussing the Warning regarding myelosuppression. This presentation minimizes the seriousness of the myelosuppresive risk. Additionally, this risk is minimized by the placement of the information between two paragraphs discussing the "most common" and "other common" side effects (359-363) and "other side effects" (375-377). DDMAC suggests placing the information regarding the Warning before the most common side effects and increasing the prominence to distinguish the Warning from the more common side effects.

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/s/

Stephanie R Victor
10/21/2008 07:52:45 AM
DDMAC REVIEWER

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, October 10, 2008 12:44 PM
To: 'Ceruzzi, Marion'
Cc: 'Karjian, Lucine'
Subject: RE: NDA 22-277 Temo IV Telecon Questions

Marion,
Part of our team had not replied to me when I indicated to you that your comments were accurate. In that light, we have the following.

1. Please justify the specification of not more than (b) (4) in the drug substance. According to the ICH guidelines, DS specifications should not be more than (b) (4) unless this impurity has been qualified in toxicology studies. Our concern is that the oral toxicology study in which (b) (4) was spiked may not qualify this impurity for IV administration.

2. (b) (4) has been qualified in the oral product at (b) (4) and in the IV product at (b) (4)

It is not clear that either (b) (4) are highly bioavailable when administered orally. Please provide evidence that these impurities/degradants are bioavailable at levels that would provide sufficient exposure in the completed toxicology studies.

Thanks,

Paul

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Wednesday, October 08, 2008 4:08 PM
To: Zimmerman, Paul F
Cc: Karjian, Lucine
Subject: NDA 22-277 Temo IV Telecon Questions

Dear Paul,

Please confirm that we have accurately captured the questions as listed below. FYI, we will be meeting with our team tomorrow morning and will get back to you after our meeting with the timing of our formal response.

1. Please justify the specification of not more than (b) (4) in the drug substance. According to the ICH guidelines, DS specifications should not be more than (b) (4) unless this impurity has been qualified in toxicology studies. Our concern is vascular pain which is described in the literature as being associated with this impurity

2. (b) (4) has been qualified in the oral product at (b) (4) What is the actual bioavailability of (b) (4) in the IV formulation solution? How does this compare to the finished product specifications of (b) (4)

Comment: Give us a comfort level in that either (b) (4) are similar enough to be bioavailable in the IV solution formulation and that any higher amounts have been qualified in toxicology studies

Regards,

Marion

MARION CERUZZI, PH.D.
Global Regulatory Affairs
Schering-Plough Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033
Phone: 908 740-2336
Fax 908 740-3583

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/s/

Paul Zimmerman

10/10/2008 12:47:40 PM

CSO

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Internal Consult

Date: October 10, 2008

To: Paul Zimmerman
Regulatory Project Manager
DDOP

From: Keith Olin, PharmD
Regulatory Review Officer
Division of Drug Marketing and Communication

Subject: NDA 22-277
DDMAC labeling comments for Temodar (Temozolomide)

DDMAC has reviewed the proposed FPI for Temodar and offer the following comments:

DDMAC notes that the label did not include PPI for this NDA.

Section	Statement from draft	Comment
Highlights of prescribing Information	• "Adjust dosage according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. BSA dosage calculations see Table 5. Capsule combinations on a daily dose, see Table 6. (2.2)"	Please consider leaving (or revising) this statement in the highlight section of the FPI and not deleting this statement completely.

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/s/

Keith Olin

10/10/2008 05:19:56 PM

DDMAC REVIEWER

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, October 09, 2008 11:09 AM
To: 'Ceruzzi, Marion'
Cc: 'Karjian, Lucine'
Subject: RE: NDA 22-277 Temo IV Telecon Questions

Marion,

This is accurate.

Thanks
Paul

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Wednesday, October 08, 2008 4:08 PM
To: Zimmerman, Paul F
Cc: Karjian, Lucine
Subject: NDA 22-277 Temo IV Telecon Questions

Dear Paul,

Please confirm that we have accurately captured the questions as listed below. FYI, we will be meeting with our team tomorrow morning and will get back to you after our meeting with the timing of our formal response.

1. Please justify the specification of not more than (b) (4) in the drug substance. According to the ICH guidelines, DS specifications should not be more than (b) (4) unless this impurity has been qualified in toxicology studies. Our concern is vascular pain which is described in the literature as being associated with this impurity

2. (b) (4) has been qualified in the oral product at (b) (4) What is the actual bioavailability of (b) (4) in the IV formulation solution? How does this compare to the finished product specifications of (b) (4)

Comment: Give us a comfort level in that either (b) (4) are similar enough to be bioavailable in the IV solution formulation and that any higher amounts have been qualified in toxicology studies

Regards,

Marion

MARION CERUZZI, PH.D.
Global Regulatory Affairs
Schering-Plough Corp.
2000 Galloping Hill Road

Kenilworth, NJ 07033
Phone: 908 740-2336
Fax 908 740-3583

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/s/

Paul Zimmerman

10/9/2008 02:29:33 PM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, October 07, 2008 10:04 AM
To: 'Ceruzzi, Marion'
Cc: 'Karjian, Lucine'
Subject: RE: NDA 22-277: Response to Q1 from Pharmcology Reviewer

Dear Marion,

It appears that the reference to batch #28396-103 in the Pharmacology/Toxicology review for NDA 21029 was a typo.

Paul

From: Ceruzzi, Marion [mailto:marion.ceruzzi@spcorp.com]
Sent: Thursday, October 02, 2008 9:10 AM
To: Zimmerman, Paul F
Cc: Karjian, Lucine
Subject: NDA 22-277: Response to Q1 from Pharmcology Reviewer

Dear Paul,

Listed below is the original Question 1 and our Response to Question 1. At this point please let us know if this adequately answers the question from the reviewer or if the reviewer requires additional information or would still like to see the information in tabulated form.

Question 1
There appears to be insufficient information to qualify (b) (4) . To aid in the qualification of these impurities/degradants, please tabulate the batch analysis from batches 78012-090, 28395-103, and 28396-103. This tabulation should specify % levels of (b) (4) and % purity of temozolomide in comparison to the specifications for the to-be-marketed drug product.

Response to Question 1

Impurities reported with temozolomide IV are (b) (4) (not more than (b) (4) in specifications of the drug product) and (b) (4) (not more than (b) (4) in specifications of the drug product). In order to qualify impurities for approval of the oral formulation of temozolomide, a one-cycle oral toxicity study in rats and genotoxicity studies (bacterial mutagenicity and chromosome aberration study) were conducted using temozolomide drug substance to which the impurities (b) (4) were added. Since AIC is a metabolite of temozolomide via MTIC and is an intrinsic compound associated with purine biosynthesis, AIC was not included in the (b) (4) qualifying studies. (b) (4) was included in the qualifying studies since it was identified as an impurity in the oral formulation; however, it has not been identified in the IV formulation. The amount of each impurity administered to rats

was 1.8 times and 1.1 times the maximum daily human intake in mg for [redacted]. Toxicity findings similar to those observed with temozolomide without added impurities were observed. Additionally, there was no difference observed in genotoxicity. For these reasons if these impurities are within specifications, no new toxicities are expected.

> The batch analysis report for batch **78012-090** used in toxicology studies for temo IV is located in Section 3.2.P.5.4 of Module 3. The stability summary and conclusions for this batch and 36-months stability data are located in 3.2.P.8.1 and 3.2.P.8.3 respectively. The batch analysis indicate that the amount of [redacted] in this batch was [redacted]. Stability data indicate that the amount of [redacted] *at 36 months was* [redacted]. Only two degradation products were observed during the stability studies: [redacted]. *No other impurities (e.g.* [redacted] were observed above the quantitation limit of [redacted] *The purity of this batch was 104.9%.*
>
> **28395-103** was an early API batch used in toxicology studies in the original capsule NDA (21-029). Batch analysis data indicate that the amount of [redacted] *and* [redacted]*, both below the qualification levels. The purity of temozolomide for this batch was 99.6%.*

The specification for [redacted] in the Temozolomide [redacted] for Injection at the end of its shelf-life is [redacted] This is considered to be qualified since the amount used in the batch used for the oral qualifying toxicology studies was [redacted] and the oral and IV formulations of temozolomide have been shown to be bioequivalent. Also, as mentioned above, [redacted] has not been identified in the temozolomide IV formulation. The specifications of the finished product (the marketed lyophilized powder for Injection) (3.2P.5.1) adequately ensure that the qualified levels of the impurities are not exceeded.

As stated earlier, we cannot locate batch **28396-103,** please clarify where this batch is located in the NDA.

Please let us know if you have any further questions on this information.

Regards,

Marion

MARION CERUZZI, PH.D.
Global Regulatory Affairs
Schering-Plough Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033
Phone: 908 740-2336
Fax 908 740-3583

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/s/

Paul Zimmerman

10/7/2008 10:06:45 AM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, September 30, 2008 8:29 AM
To: 'Ceruzzi, Marion'
Subject: NDA 22-277 for Temodar - Pharmacology

Dear Marion,

We have the following requests. Please confirm receipt and reply as soon as possible.

1. There appears to be insufficient information to qualify (b) (4) . To aid in the qualification of these impurities/degradants, please tabulate the batch analysis from batches 78012-090, 28395-103, and 28396-103. This tabulation should specify % levels of (b) (4) and % purity of temozolimide in comparison to the specifications for the to-be-marketed drug product.

2. The exact composition of the "placebo" is not clear from the study reports for studies 01350, 02042, 02044, 02267, and 02510. Please provide a qualitative and quantitative description of the components of this formulation.

Thanks,
Paul

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/s/

Paul Zimmerman

9/30/2008 08:32:19 AM

CSO

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: August 12, 2008

FROM: Xikui Chen, Ph.D.
John A. Kadavil, Ph.D.
Jacqueline A. O'Shaughnessy, Ph.D
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-277, Temodar (Temozolomide) (b) (4) for Injection, 100 mg/vial, Sponsored by Schering Corporation

TO: Robert Justice, MD
Director, Division of Drug Oncology Products (DDOP)

As requested by DDOP, the Division of Scientific Investigations audited records of clinical conduct for two clinical investigator sites and the analytical portion of the following multi-center bioequivalence study:

> **Protocol P02467:** SCH 52365: A Bioequivalence Trial of Oral and Intravenously Administered Temozolomide in Patients with Primary CNS Malignancies

The review division requested that DSI audit clinical study records for two of the clinical sites that participated in this multi-center study. The following clinical sites were inspected:

> Max Schwarz, M.D.
> Centre for Clinical Studies, Melbourne, Australia
>
> Maria G. Pallota, M.D.
> Hospital Italiano-Sociedad Italiana De Beneficencia en Buenos Aires, Buenos Aires, Argentina

The analytical portion of Study P02467 was conducted at (b) (4)

Following the inspections at the clinical sites (Dr. Schwarz, 6/16-20/08 and Dr. Pallota, 6/23-27/08), no significant deficiencies were found. Form 483 was not issued at either site. Following the inspection of (b) (4) (b) (4) Form 483 was issued. Our review of the objectionable findings follows.

Analytical Site: (b) (4)

1. **The incurred sample reproducibility (ISR) criterion supplied by the sponsor for Study P02467 does not reflect the performance of the analytical method.**

As required by the sponsor, (b) (4) reassayed 10% of the study samples to evaluate ISR. Schering's criteria stated that incurred sample repeats are considered acceptable if the original and reassay values from (b) (4) of the repeated samples have a relative percent difference (RPD) (b) (4) However, an ISR criterion of RPD (b) (4) is liberal considering that the assay performance during method validation and study conduct was tight (≤10% CV for temozolomide). Although the sponsor needs to have an ISR criterion that is reflective of assay performance, a majority of the samples reanalyzed in the study were reproducible in that only 19% of the incurred sample repeats for temozolomide, and 25% for the MTIC metabolite, had an RPD that exceeded (b) (4).

2. **An investigation of the high failure rate of analytical runs in Study P02467T (temozolomide) was not conducted although 33% (5 of 15) of the runs failed to meet the acceptance criteria for standards or QCs.**

Although there was no documentation to indicate that the high failure rate was evaluated, the firm claimed that they monitored the study conduct closely. The firm's current procedures require an investigation if more than 25% of the total anticipated runs are rejected for a given study.

3. **Failure to document all aspects of study conduct. For example:**
   a. **The lot of matrix used for the calibration standards in Studies P02467T (temozolomide) and P02467M (MTIC) was not documented at the time the calibration standards were prepared for each analytical run.**

At the start of sample analysis, the firm identified a lot of matrix to be used in preparing freshly spiked calibration standards for each batch. Although there was no documentation on each day of spiking to confirm that the pre-identified lot

was used, the analytical procedure forms did specify that human plasma should be used.

b. The analytical procedure for MTIC required that a maximum of (b) (4) samples be extracted at a time. There was no documentation to confirm that the procedure was followed or to identify the samples processed in each subset of samples in a run.

Small processing subsets were required due to stability concerns regarding the MTIC metabolite. Although the firm claimed that the procedure was followed, the source data does not confirm which samples were processed together and whether a QC was included in each subset. However, one analyst processed all the samples in a run.

c. There was no documentation to confirm that the autosampler injection sequence was verified.

The firm claimed that the sample sequence was checked but not documented in writing.

With respect to items 3a-c, the firm needs to improve their documentation practices to confirm that all aspects of study conduct are carried out appropriately.

Conclusion:

Following the above inspections, DSI recommends that the clinical (Drs. Schwarz and Pallota) and analytical portions of Study P02476 be accepted for review.

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

Xikui Chen, Ph.D.

John A. Kadavil, Ph.D.

Jacqueline A. O'Shaughnessy, Ph.D.

Final Classifications:
NAI - Schwarz
NAI - Pallota
VAI – (b) (4)

cc:
DSI/Vaccari/Patague
DSI/Chen/Kadavil/O'Shaughnessy/Viswanathan/Yau
DDOP/Tammie Brent-Steele
OCP/DCP5/Booth/Abraham
HFR-PA150/McGirl
HFR-SW1580/Stone
Draft: JAO/JAK/XC
Edit: SS 8/1/08
File:5377; O:\BE\EIRCOVER\22277sch.tem

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/s/

John Kadavil
8/12/2008 03:39:19 PM
PHARMACOLOGIST
Dr. Viswanathan signed the paper copy on 8/12/08. Dr. Kadavil signed for Drs. Chen and O'Shaughnessy. Hard copies available upon request.

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, August 07, 2008 3:34 PM
To: 'Karjian, Lucine'
Cc: 'Ceruzzi, Marion'
Subject: NDA 22-277 for Temodar - CMC

Dear Lucine,

Regarding NDA 22,277 we have the following comments. Please respond as soon as possible.

Drug Substance:

The following comment pertains to the drug substance analytical tests for the detection of process related impurities.

1. Provide the Level of Detection (LOD) and the Level of Quantitation (LOQ) for the analytical methods that were used to measure the level of the following drug substance manufacturing process related impurities: (b) (4)

Drug Product:

2. It is indicated that Temozolomide is (b) (4) in the lyophilized powder formulation, with a mixture of predominantly (b) (4) Explain how you determined the (b) (4) state of the drug substance and please provide this data to the NDA.

3. Modify the "Initial Stability Protocol" to include the following additional tests:
   - Test the vials on stability, from the three initial production batches, for "Sterility" and "Endotoxins" at long term storage condition (5C ± 3C) at 12 months time point. This will be in addition to the already indicated 24 and 36 months time points for these two tests.

   - The "Reconstitution Time" tests to be performed on vials stored on long term storage condition (5C ± 3C) and test the vials at 6, 12, 24, and 36 months stability time points.

4. Modify the "Ongoing Stability Protocol" to include the following additional tests:
   - The vials from one production batch at each year that is placed on stability protocol, be tested for the reconstitution time, endotoxins, and sterility on long term storage condition (5C ± 3C) at 6, 12, 24, and 36 months stability time points.

5. Please provide the Structured Product Labeling (SPL) Drug Listing Data Element.

Thanks
Paul

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/s/

Paul Zimmerman

8/7/2008 03:38:22 PM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, July 10, 2008 12:16 PM
To: 'Karjian, Lucine'
Cc: 'Ceruzzi, Marion'
Subject: NDA 22-277 for Temozolomide- Microbiology information request

Dear Lucine,

Regarding NDA 22-277 we have the following Microbiology information request.

NDA 22-277
Temodar (b) (4) for Injection
Product Quality Microbiology Information Request

(b) (4)

Thanks,
Paul

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/s/

Paul Zimmerman

7/10/2008 12:23:34 PM

CSO

Zimmerman, Paul F

From: Karjian, Lucine [lucine.karjian@spcorp.com]
Sent: Wednesday, May 28, 2008 9:24 AM
To: Zimmerman, Paul F
Subject: RE: NDA 22-277 for Temodar - CMC
Attachments: Stability Tables.pdf; emfalert.txt

Dear Paul,

Chemical stability data for temozolomide drug substance was provided in section 4.A.4.2 of the approved NDA 21-029. In addition and as requested, attached are stability tables containing 36 months of chemical stability data for three recent batches of temozolomide drug substance. These batches are: 04-185-212V (Table 1), 04-185-213V (Table 2), and 04-185-214V (Table 3).

Please note that Microbial Limit and Bacterial Endotoxins stability data for the above batches, identified as 55357-121/**04-185-212V**, 55357-121/**04-185-213V**, and 55357-121/**04-185-214V**, are provided in section 3.2.S.7.3 of NDA 22-277.

This data is provided to the FDA reviewer as a desk copy--for information only. We commit to amending the approved NDA for Temodar Capsules, 21-029, to include this data, as well as any additional chemical stability data that becomes available at the time of the annual report filing, due in October 2008.

Please let me know if there are any additional comments or questions for NDA 22-277 related to CMC.

Best regards,
Lucine Karjian
Global Regulatory Affairs-CMC
(908) 740-5224

> -----Original Message-----
> **From:** Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
> **Sent:** Tuesday, May 27, 2008 4:11 PM
> **To:** Karjian, Lucine
> **Subject:** NDA 22-277 for Temodar - CMC
>
> Dear Lucine,
>
> Regarding NDA 22-277 for Temodar, we have the following
> **Comment to the Applicant Regarding Drug Substance (DS) Stability Data:**
> Provide appropriate stability data for the drug substance to NDA 22-277, or indicate the details of annual report submissions (date of submission, page numbers, etc.) to NDA 21-029, which include most recent stability data.
>
> Thanks,
> Paul

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/s/

Paul Zimmerman

5/28/2008 09:33:35 AM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, May 27, 2008 4:11 PM
To: 'Karjian, Lucine'
Subject: NDA 22-277 for Temodar - CMC

Dear Lucine,

Regarding NDA 22-277 for Temodar, we have the following

Comment to the Applicant Regarding Drug Substance (DS) Stability Data:

Provide appropriate stability data for the drug substance to NDA 22-277, or indicate the details of annual report submissions (date of submission, page numbers, etc.) to NDA 21-029, which include most recent stability data.

Thanks,
Paul

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/s/

Paul Zimmerman

5/27/2008 04:13:11 PM

CSO

Zimmerman, Paul F

From: Karjian, Lucine [lucine.karjian@spcorp.com]
Sent: Thursday, May 15, 2008 3:33 PM
To: Zimmerman, Paul F
Cc: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar- CMC
Attachments: response-temo iv-may 2008.pdf; emfalert.txt

Dear Paul,

In order to provide a comprehensive response, I have included FDA comments from May 13 and 14, 2008. As agreed this morning, I will follow up and file the response as information amendment to NDA 22-277.

2. Provide drug substance specifications as well as Certificate of Analysis for a typical batch of the drug substance to be used in the manufacture of the drug product. (FDA comment from 5/13)

SP response: A representative CoA for a drug substance lot used in the manufacture of one drug product batch was provided in 3.2.R.1.P Executed Production Records. The drug substance chemical testing specifications are as approved in NDA 21-029. The additional specifications for micro testing was provided in 3.2.S.4.1 (NDA 22-277). We can provide the specification page of the drug substance that include both chemical and microbiological testing requirements within approximately one week. Would this be satisfactory?

FDA response: Yes. Provide the updated drug substance specification sheet to NDA 22-277. (FDA comment from 5/14)

SP Response: Attached is the consolidated specification page that includes specifications approved in NDA 21-029, as well as the additional specifications in 3.2.S.4.1 of NDA 22-277 (attachment 1). Also attached for reference and convenience, is the drug substance specification page from the approved NDA 21-029 for the capsules (attachment 2).

3. Provide stability data for the drug substance batches to be used in the manufacture of the drug product for the NDA. Alternatively, update the NDA 21-029 with stability data for the drug substance. (FDA comment from 5/13)

SP Response: We propose to update NDA 21-029 via the annual report due in October 2008. Data for 36-months for three drug substance batches will be provided in the annual report. Would this be satisfactory?

FDA response: No. Provide drug substance stability data to NDA 22-277 as soon as possible. You also need to provide this data to NDA 21-029 annual report in October 2008. (FDA comment from 5/14)

SP Response: The temozolomide drug substance used in the capsule and intravenous formulation is identical and follows the same manufacturing steps and chemical testing as described in the approved Temodar Capsule NDA 21-029. Temozolomide drug substance used in the intravenous formulation is tested additionally for Microbial Limits and Bacterial Endotoxins. The chemical stability of temozolomide drug substance has previously been demonstrated in NDA 21-029. In order to support microbiological stability, data on three batches for Microbial Limits and Bacterial Endotoxins at initial,

12 months and 24 months was provided in 3.2.S.7.3 of NDA 22-277. We intend to update this section to add Microbial Limit and Bacterial Endotoxins data at 36 months as it becomes available.

In light of the response above to #3, please advise and clarify FDA comment from 5/14/08 above.

Thank you and regards,

Lucine Karjian

Tel: 908-740-5224

-----Original Message-----
From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Wednesday, May 14, 2008 3:37 PM
To: Karjian, Lucine
Cc: Ceruzzi, Marion
Subject: NDA 22-277 for Temodar- CMC

Dear Lucine,

We have the following responses from our CMC reviewer.

A representative CoA for a drug substance lot used in the manufacture of one drug product batch was provided in 3.2.R.1.P Executed Production Records. The drug substance chemical testing specifications are as approved in NDA 21-029. The additional specifications for micro testing was provided in 3.2.S.4.1 (NDA 22-277). We can provide the specification page of the drug substance that include both chemical and microbiological testing requirements within approximately one week. Would this be satisfactory?

FDA response: Yes. Provide the updated drug substance specification sheet to NDA 22-277.
We propose to update NDA 21-029 via the annual report due in October 2008. Data for 36-months for three drug substance batches will be provided in the annual report. Would this be satisfactory?

FDA response: No. Provide drug substance stability data to NDA 22-277 as soon as possible. You also need to provide this data to NDA 21-029 annual report in October 2008.

Thanks,
Paul

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/s/

Paul Zimmerman
5/16/2008 09:24:00 AM
CSO

Zimmerman, Paul F

From: Karjian, Lucine [lucine.karjian@spcorp.com]
Sent: Wednesday, May 14, 2008 9:17 AM
To: Zimmerman, Paul F
Cc: Ceruzzi, Marion
Subject: RE: NDA 22-277 for Temodar
Attachments: emfalert.txt

Dear Paul,

Thank you for your follow up and for providing comments. Below are SP responses to the comments:
1. The Drug Establishment Numbers are:

- (b) (4)
- Schering-Plough, Brinny, Ireland (API release site): 3002808087
- (b) (4)
- Schering Corporation, Florida, USA (Drug product secondary packaging and release site): 1010370

2. A representative CoA for a drug substance lot used in the manufacture of one drug product batch was provided in 3.2.R.1.P Executed Production Records. The drug substance chemical testing specifications are as approved in NDA 21-029. The additional specifications for micro testing was provided in 3.2.S.4.1 (NDA 22-277). We can provide the specification page of the drug substance that include both chemical and microbiological testing requirements within approximately one week. Would this be satisfactory?

3. We propose to update NDA 21-029 via the annual report due in October 2008. Data for 36-months for three drug substance batches will be provided in the annual report. Would this be satisfactory?

Please advise if the above responses and resolutions to the comments below are satisfactory. Also, please let me know if there are any additional CMC comments or questions.

Thank you and regards.
Lucine
908-740-5224

> -----Original Message-----
> **From:** Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
> **Sent:** Tuesday, May 13, 2008 11:45 AM
> **To:** Karjian, Lucine
> **Cc:** Ceruzzi, Marion
> **Subject:** NDA 22-277 for Temodar
>
> Dear Lucine,
>
> Regarding your comment concerning methods validation, our CMC team notes that at this time we do not have comments. However, we have the following comments from our CMC team.
>
> 1. Provide the CFN numbers for all of the sites that require inspection and have been noted in the NDA. These sites are listed on the 356 form as well as in the manufacturing sections for the drug substance and the drug product.
> 2. Provide drug substance specifications as well as Certificate of Analysis for a typical

batch of the drug substance to be used in the manufacture of the drug product.

3. Provide stability data for the drug substance batches to be used in the manufacture of the drug product for the NDA. Alternatively, update the NDA 21-029 with stability data for the drug substance.

Thanks,
Paul

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/s/

Paul Zimmerman

5/14/2008 09:26:11 AM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, May 14, 2008 3:37 PM
To: 'Karjian, Lucine'
Cc: 'Ceruzzi, Marion'
Subject: NDA 22-277 for Temodar- CMC

Dear Lucine,

We have the following responses from our CMC reviewer.

A representative CoA for a drug substance lot used in the manufacture of one drug product batch was provided in 3.2.R.1.P Executed Production Records. The drug substance chemical testing specifications are as approved in NDA 21-029. The additional specifications for micro testing was provided in 3.2.S.4.1 (NDA 22-277). We can provide the specification page of the drug substance that include both chemical and microbiological testing requirements within approximately one week. Would this be satisfactory?

FDA response: Yes. Provide the updated drug substance specification sheet to NDA 22-277.

We propose to update NDA 21-029 via the annual report due in October 2008. Data for 36-months for three drug substance batches will be provided in the annual report. Would this be satisfactory?

FDA response: No. Provide drug substance stability data to NDA 22-277 as soon as possible. You also need to provide this data to NDA 21-029 annual report in October 2008.

Thanks,
Paul

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/s/

Paul Zimmerman

5/14/2008 03:40:25 PM

CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, May 13, 2008 11:45 AM
To: 'Karjian, Lucine'
Cc: 'Ceruzzi, Marion'
Subject: NDA 22-277 for Temodar

Dear Lucine,

Regarding your comment concerning methods validation, our CMC team notes that at this time we do not have comments. However, we have the following comments from our CMC team.

1. Provide the CFN numbers for all of the sites that require inspection and have been noted in the NDA. These sites are listed on the 356 form as well as in the manufacturing sections for the drug substance and the drug product.

2. Provide drug substance specifications as well as Certificate of Analysis for a typical batch of the drug substance to be used in the manufacture of the drug product.

3. Provide stability data for the drug substance batches to be used in the manufacture of the drug product for the NDA. Alternatively, update the NDA 21-029 with stability data for the drug substance.

Thanks,
Paul

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/s/

Paul Zimmerman

5/13/2008 11:48:53 AM

CSO

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: March 12, 2008

TO: Dr. C.T. Viswanathan
Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Robert Justice, MD, Director, Review Division, HFD-150

FROM: Tammie Brent, Regulatory Project Manager, HFD-150

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-277
Temodar (Temozolomide) IV 100mg/vial

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
P02467	**Hospital Italiano de Buenos Aires**, Gascón 450, (C1181ACH); Capital Federal, Argentina PI Dra. Maria Guadalupe Pallotta +(5411) 04959-0200 Ph. Maria.pallotta@hospitalitaliano.org.ar Site Coordinator :Viviana Videla +(5411) 4959-0200 ext.8159 Ph. +(5411) 4959-0497/0426 Fax vm.videla@gmail.com	(b) (4)
P02467	Centre for Clinical Studies, Bianca Scott, Study Coordinator Ph: 03 9207 1925	(b) (4)

	Fax: 03 9207 1940 Email: B.Scott@nucleusnetwork.com.au Postal Address: Centre for Clinical Studies, Nucleus Network PO Box 6083 St. Kilda Road Central Melbourne 8008 VIC Australia Street Address: Centre for Clinical Studies, Nucleus Network 5th Floor Bumet Tower AMREP Precinct 89 Commercial Road Melbourne 3004 Victoria	

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

__X__ There is a lack of domestic data that solely supports approval;

___x__ Other (please explain): Data is pivotal to future approval action

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **June 20, 2008**. We intend to issue an action letter on this application by **November 24, 2008**.

Should you require any additional information, please contact Tammie Brent.

Concurrence: (Optional)
Brian Booth, PhD ClinPharm Team Leader
Sophia Abraham, PhD ClinPharm Reviewer

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/s/

Brian Booth

3/28/2008 02:43:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-277

Schering Corporation
Attention: Marion Ceruzzi, Ph.D., Sr. Manager, Global Reg. Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Ceruzzi:

Please refer to your new drug application (NDA) dated January 23, 2008, received January 24, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Temodar (Temozolomide) (b) (4) for Injection 100mg/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is November 24, 2008.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients.

If you have any questions, call Tammie Brent, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Robert Justice, MD
Director
Division of Drug Oncology Products
Center for Drug Evaluation and Research

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/s/

Robert Justice

3/21/2008 04:18:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-277

NDA ACKNOWLEDGMENT

Schering Corporation
Attention: Marion Ceruzzi, Ph.D., Sr. Manager, Global Reg. Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Ceruzzi:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Temodar (Temozolomide) (b) (4) for Injection 100mg/vial

Date of Application: January 23, 2008

Date of Receipt: January 24, 2008

Our Reference Number: NDA 22-277

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 24, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Tammie Brent, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Tammie Brent, RN MSN
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Tammie Brent-Steele

3/21/2008 03:57:41 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-277 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Temodar
Established Name: Temozolomide
Strengths: 100mg/vial

Applicant: Schering Corporation
Agent for Applicant (if applicable):

Date of Application: January 23, 2008
Date of Receipt: January 24, 2008
Date clock started after UN:
Date of Filing Meeting: March 11, 2008
Filing Date: March 24, 2008
Action Goal Date (optional): User Fee Goal Date: Nov. 24, 2008

Indication(s) requested: Newly diagnosed GBM and Refractory anaplastic astrocytoma

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 21-029 for Temodar Capsules, exclusivity expires, 3-15-2012.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☐ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? YES If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers:

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☒

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒

- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 11, 2008

NDA #: 22-277

DRUG NAMES: Temodar (Temozolomide) (b) (4) for Injection

APPLICANT: Schering Corp.

BACKGROUND: The oral formulation of Temodar is approved in the United States for adult patints with newly diagnosed glioblastoma multiforme (GBM) and in adult patients with refractory anaplastic astrocytoma. This new NDA is for Temodar (b) (4) for Injection for IV administration.

ATTENDEES: Justice, Robert; Farrell, Ann T; Cohen, Martin H; Rosenfeldt, Hans; Verbois, Leigh; Tang, Shenghui; Booth, Brian P; Abraham, Sophia; Sarker, Haripada

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Martin Cohen, MD
Statistical:	Shenghui Tang, PhD
Pharmacology:	Hans Rosenfeldt, PhD
Chemistry:	Jila Boal, PhD
Microbiology:	Bryan Riley, PhD
Clinical Pharmacology:	Sophia Abraham, PhD
DSI:	TBD
Regulatory Project Management:	Tammie Brent, RN, MSN
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

CLINICAL PHARMACOLOGY FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☒ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Tammie Brent RN, MSN
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Tammie Brent-Steele

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CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Jim McVey HFD-805
Microbiology Consult for NDA 22-277

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Tammie Brent
Regulatory Project Manager
301-796-1409 Bldg. 22 Rm. 2175

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3-19-08		22-277	NDA	1-23-08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Temodar (b) (4) for injection			6-1-08

NAME OF FIRM: Schering Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology consult for NDA 22-277 requested per Haripada Sarker, PhD. for evaluation of test method and specification related to DS and DP sterility, and any other related microbial issues. The NDA submission may be found in the electronic document room dated 1-23-08. Standard review, due date November 24, 2008. Link: \\Cdsesub1\evsprod\NDA022277\0000 Please Tammie Brent, project manager for any questions. Contact information above.

SIGNATURE OF REQUESTOR
Tammie Brent RN, MSN RPM

METHOD OF DELIVERY (Check one)
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/s/

Tammie Brent-Steele

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Janet Anderson, Project Manager
DMETS/DSRCS
WO22 RM3435 HFD-095
301-796-0675

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Tammie Brent, Project Manager
Division of Oncology Drug Products
WO 22 Rm. 2175
301-796-1409

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-15-08		22-277	New NDA	1-23-08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Temodar (Temozolomide)			April 30, 2008

NAME OF FIRM: Schering Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
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- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
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- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: New NDA for Temodar (b) (4) for Injection. Submission received 1-24-08, filing date 3-24-08, mid-cycle meeting TBD, PDUFA date TBD, if priority, 7-24-08, if standard, 11-24-08. DDOP request review of Package insert labeling and patient labeling contained in the sNDA submission. The submission can be found in the EDR, dated 1-23-08. Carton and container labeling can be found in module one of the submission. Clinical reviewer: Martin Cohen, MD. For any questions, please contact the Project Manager: Tammie Brent.

SIGNATURE OF REQUESTOR
Tammie Brent, Project Manager, 301-796-1409

METHOD OF DELIVERY (Check one)
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/s/

Tammie Brent-Steele

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
DDMAC
Attention: JuWon Lee
WO22 Rm. 1493
301-796-1200

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Tammie Brent
Regulatory Project Manager
DDOP
WO22 Rm. 2175
301-796-1409

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2-15-08		22-277	New NDA	1-23-08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Temodar (Temozolomide)			April 30, 2008

NAME OF FIRM: Schering Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
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- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DDOP request DDMAC review the proposed product labeling and any relevant advertising for this NDA. Please see the submission in the Electronic Document Room dated 1-23-08 for product label and documents. PDUFA date TBD, if priority, 7-24-08, if standard, 11-24-08. Clinical Reviewer: Martin Cohen, MD For any questions, please contact the Project Mgr: Tammie Brent.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Tammie Brent	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
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/s/

Tammie Brent-Steele

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