CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022453Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22453 SUPPL # HFD #

Trade Name Topotecan Injection

Generic Name N/A

Applicant Name Teva Pharmaceuticals USA

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 ☐

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

505(b)(2)

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.

N/A

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:

N/A

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 *for this Sponsor*?

YES ☐ NO ☒

Note: The innovator (GSK) has pediatric exclusivity through April 7, 2015 for the ovarian indication, which TEVA is not seeking.

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?

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#	020671	Hycamtin (topotecan hydrochloride) Injection/GSK
NDA#	020981	Hycamtin (topotecan) Capsules/ GSK
NDA#	200582	Topotecan Injection/Hospira
NDA#	200199	Topotecan Injection/Sandoz

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: Deanne Varney
Title: Regulatory Project Manager
Date: 12/3/2012

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, DOP2

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DEANNE R VARNEY
12/03/2012

PATRICIA KEEGAN
12/04/2012

1.3.3 DEBARMENT CERTIFICATION

In accordance with the FD&C Act 306(k)(1), Teva Parenteral Medicines, Inc. certifies that we did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Act, in connection with this application.

{See appended electronic signature page}

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

NDA/BLA#: 22-453 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: PDUFA Goal Date: October 18, 2009 Stamp Date: December 18, 2008

Drug Oncology Products

Proprietary Name: Topotecan Hydrochloride Injection

Established/Generic Name: Topotecan Hydrochloride Injection

Dosage Form: Injection

Applicant/Sponsor: Teva Parenteral Medicines, Inc.

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: #1: Small cell lung cancer sensitive disease after failure of first-line chemotherapy.

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 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 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: Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amendable to curative treatment with surgery and/or readiation therapy.

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)

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

/s/

Susan Jenney
6/24/2009 11:11:03 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22453 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Topotecan Injection Dosage Form: Injection		Applicant: Teva Pharmaceuticals, USA Agent for Applicant (if applicable):
RPM: Deanne Varney		Division: DOP2

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20671 – Hycamtin (topotecan hydrochloride) Injection, 4mg/vial

Provide a brief explanation of how this product is different from the listed drug.

Change in dosage form (Hycamtin is a lyophilized powder, the proposed product is a liquid solution)

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 12/20/2012

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 12/25/2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR: 10/16/2009

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☒ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent expired: November 28, 2010. Patent had not expired during first review cycle, so a paragraph III certification was required.
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

✓ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval: 12/20/2012 CR: 10/16/2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12/19/2012
• Original applicant-proposed labeling	6/25/2012 - resubmission 12/18/2008 - original
• Example of class labeling, if applicable	Hycamtin 3/26/2010

[4] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	N/A
• Original applicant-proposed labeling	N/A
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	12/19/2012
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 3/11/2009 ☒ DMEPA 7/9/09, 11/16/12, and 12/19/2012 ☐ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) 11/29/12 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Review: 2/29/09
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 11/15/2012
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 12/20/2012
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 6/24/09 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	12/20/2012 12/19/2012 12/13/2012 (uploaded 12/20/2012) 12/11/2012 12/4/2012 11/16/2012 11/7/2012 (uploaded 11/13/2012) 10/1/2012 9/26/2012 9/13/2012 7/5/2012 8/19/2009 8/12/2009 7/10/2009 5/20/2009 2/27/2009 1/7/2009
❖ Internal memoranda, telecons, etc.	11/26/2012 10/3/2012 9/5/2012 7/18/2012
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11/14/2008
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 1/4/2013 (uploaded 1/15/2013) 10/16/2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/20/2012
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	8/26/09 see Clinical Review
• Clinical review(s) *(indicate date for each review)*	9/27/12

[6] Filing reviews should be filed with the discipline reviews.

	8/26/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☒ None	
Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 10/3/12 see clin pharm review 8/28/09
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/3/12, 8/28/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None

Nonclinical ☐ None	
✓ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 10/17/12 concurrence with pharm tox review 9/17/09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/17/12, 9/17/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 10/14/09,
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/20/12, 12/04/12, 8/31/12, 8/31/09, 2/17/09
Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 10/24/12, 7/13/09, 1/26/09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☒ Review & FONSI *(indicate date of review)*	5/19/09
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 8/31/12 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

Varney, Deanne

From: Hughes, Monica L
Sent: Wednesday, December 19, 2012 1:35 PM
To: Cory.Wohlbach@tevapharm.com
Cc: Philip.Erickson@tevapharm.com; Varney, Deanne
Subject: Topotecan NDA 22453

Hello Cory,

On behalf of Deanne Varney, please find attached the fifth round of FDA edits to the PI for NDA 22453. The only changes in this version are in the How Supplied section. Please review these edits and let Deanne Varney know by **10AM tomorrow, Thursday, December 20th,** if the edits are acceptable.

If Teva agrees with all of the FDA proposed edits, please accept all changes and submit the final draft labeling to the NDA, and send a courtesy copy to Deanne Varney via email.

Please confirm receipt of this email communication.

Thank you,
Monica

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849
Email: monica.hughes@fda.hhs.gov

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/s/

DEANNE R VARNEY
12/19/2012

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, December 13, 2012 4:18 PM
To: Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
Subject: NDA 22453 PI Edits

Hello Cory,

Please find attached the fourth round of FDA edits on the PI for NDA 22453. This version contains only two changes, both within the Highlights. Please review these edits and let me know by **10AM tomorrow, Friday, December 14th**, if the edits are acceptable or if your team has any additional edits. If you have additional edits to propose, please accept all edits that do not require further discussion, make any additional edits in track changes, and return to me via email as well as submit clean and tracked versions to the NDA.

If Teva agrees with all of the FDA proposed edits, please accept all changes and submit all final draft labeling to the NDA.

PI:

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/20/2012

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, December 11, 2012 4:18 PM
To: Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
Cc: Philip.Erickson@tevapharm.com
Subject: NDA 22453 - FDA Edits to PI

Hello Cory,

Please find attached the third round of FDA edits on the PI for NDA 22453. We do not have any additional comments on the carton and container labeling. Please review these edits and let me know by **COB tomorrow, Wednesday, December 12th**, if the edits are acceptable or if your team has any additional edits. If you have additional edits to propose, please accept all edits that do not require further discussion, make any additional edits in track changes, and return to me via email as well as submit clean and tracked versions to the NDA.

If Teva agrees with all of the FDA proposed edits, please accept all changes and submit all final draft labeling to the NDA.

PI:

Please confirm receipt of this communication and let me know if you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/11/2012

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, December 04, 2012 2:20 PM
To: Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
Cc: Philip.Erickson@tevapharm.com
Subject: NDA 22453 - FDA Edits to Labeling

Hello Cory,

Please find attached the second round of FDA edits on the PI for NDA 22453. We also have one additional comment on the container label. Please review these edits and comments, and let me know by **COB on Thursday, December 6th**, if the edits are acceptable or if your team has any additional edits. If you have additional edits to propose, please accept all edits that do not require further discussion, make any additional edits in track changes, and return to me via email as well as submit clean and tracked versions to the NDA.

If Teva agrees with all of the FDA proposed edits, please accept all changes and submit the final draft labeling to the NDA.

PI:

Container Label:
Move the statement "Must dilute before intravenous infusion" from the side panel to the bottom of the principal display panel to increase the prominence of the statement.

Please confirm receipt of this communication and let me know if you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/04/2012

NDA REVIEW WRAP-UP MEETING MINUTES
November 26, 2012

505(b)(2) NDA 22453 (Class 2 Resubmission)
Topotecan Hydrochloride Injection, 1 mg base/mL
Teva Pharmacueticals USA

Purpose: Response to October 16, 2009 CR letter. Provides additional CMC information to resolve cGMP-related issues, final labeling, and a safety update. All other disciplines previously determined application to be approvable.

Teva is relying on GlaxoSmithKline's Hycamtin® as the previously approved drug under NDA 20-671. The reference listed drug is manufactured as a lyophilized powder and is available in 4 mg single-dose vials. Teva's proposed drug product will be supplied as an injectable solution containing 1 mg base/mL; 4 mL fill in a 6 mL vial.

Application Receipt Date: June 25, 2012

Review Team:
Deanne Varney, Regulatory Project Manager
Shakun Malik, Medical Officer/Clinical Reviewer
John Johnson, CDTL
Dubravka Kufrin, Nonclinical Reviewer
Ruby Leong, Clinical Pharmacology Reviewer
Debasis Ghosh, Quality Reviewer
Elsbeth Chikhale, Biopharmaceutics Reviewer
Denise Miller, Microbiology Reviewer
Carole Broadnax, DPDP Reviewer
Karen Munoz, DCDP Reviewer

Agenda Items:

1. **Review Upcoming Dates/Milestone**:

   - **Goal Date**: **12/14/2012**

2. **Signed Review Status**

   - CMC: The primary review will be uploaded in DARRTS on 11/27/12
   - CDTL: The CMC CDTL review will be complete by 12/7/12
   - Facility: The sites are acceptable in EES. Facilities to check for any changes in status prior to approval action
   - Biopharmaceutics: Biowaiver granted; approvable (8/31/12)

- Pharm/Tox: Review uploaded 10/17/12
- Clinical: Review uploaded 9/27/12
- Clin/Pharm: Review uploaded 10/3/12
- Microbiology: Review uploaded 10/24/12
- OPDP: In progress
- OSE: Review uploaded 11/16/12

3. **Labeling:**

   - FDA edits sent to Teva on 11/16/2012. Requested response by COB on 11/26/2012.
   - Substantially complete PI sent to OPDP 11/16/2012. OPDP will wait to review the carton and container labeling until revised mock-ups are received from Teva.

4. **Action Package:** Will provide to CPMS for review by 11/29/2012

5. **Exclusivity Summary:** In progress, with CPMS for review

6. **PMR/PMC:** None.

7. **Press Release/ASCO Burst:** No.

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/s/

DEANNE R VARNEY
11/26/2012

Varney, Deanne

From: Varney, Deanne
Sent: Friday, November 16, 2012 1:41 PM
To: Philip.Erickson@tevapharm.com; Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
Subject: NDA 22453 - Labeling Edits

Hello Drs. Erickson and Wohlbach,

Please find attached FDA edits and comments to the labeling (PI, carton and vial labels) under NDA 22453. Also attached is a figure that provides an edit to the chemical structure presented in the PI. And further below are the written comments regarding the carton and vial label.

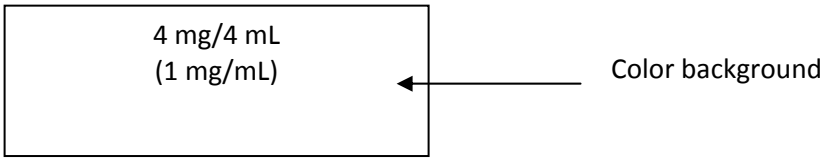
Please review this proposed labeling and, by COB on **Monday, November 26th**, let me know if the proposed edits are acceptable, or if your team has additional edits. If you have additional edits to propose, please accept all edits that do not require further discussion, make any additional edits in track changes, and return to me via email as well as submit clean and tracked versions to the NDA.

If Teva agrees with all of the FDA proposed edits, please accept all changes and submit the final draft labeling to the NDA.

Please confirm receipt of this communication and let me know if you have any questions.

1. Carton and Tray Liner Labeling and Container Label

a. Ensure the color background includes the strength statement "1 mg/mL" located directly below the statement "4 mg/4 mL" each place it is presented. For example:



b. Ensure an area for expiration date and lot number is provided on the label.

c. The NDC numbers need to be different for each packaging configuration to distinguish each product configuration and comply with the bar code rule 21 CFR 201.25. Ensure that each packaging configuration has a different NDC number and include the number on the revised label and labeling.

d. On the carton labeling, incorporate the statement "Discard Unused Portion" to appear immediately after or under the statement "Single (b) (4) Vial". Additionally, revise the statement "Single (b) (4) Vial" to read "Single Use Vial".

e. Add the statement "Single Use Vial; Discard Unused Portion" to the top of the side panel on the container label. Consider deleting the statement "Each mL contains…" if additional space is needed.

f. On the tray liner, revise the statement "5 Single (b) (4) Vials" to read "5 Single Use Vials; Discard Unused Portion"

2. **Carton and Tray Liner Labeling**

a. To increase the prominence of the storage statement, "Add a box with a black line around the storage statement and use bold red font for the letters in the statement. Additionally, revise the storage statement to read "Store refrigerated between 2ºC and 8ºC (36ºF and 46 ºF). Protect from light.

For example:

> **Store refrigerated between 2ºC and 8ºC (36ºF and 46 ºF). Protect from light.**

b. To increase the prominence of the storage statement, move the statement from the side panel to the principal display panel. The storage statement should appear below the statements "For Intravenous Use" and "Must be diluted before use." In order to make room for the storage statement on the principal display panel, consider deleting the statement "Each mL contains topotecan hydrochloride…" This statement is redundant as it is also conveyed on the side panel.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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DEANNE R VARNEY
11/16/2012

Varney, Deanne

From: Philip Erickson <Philip.Erickson@tevapharm.com>
Sent: Wednesday, November 07, 2012 10:11 PM
To: Varney, Deanne
Cc: Cory Wohlbach
Subject: Fw: NDA 22453

Dear Ms. Varney,
Please see the attached response to your earlier email. Both of your questions are addressed. Please note that I hereby authorize you to contact Cory Wohlbach directly with regard to official communications on this pending application.
Best Regards,
Phil

From: Cory Wohlbach
Sent: Wednesday, November 07, 2012 05:23 PM
To: Philip Erickson
Subject: RE: NDA 22453

Hello Phil,

1. Teva does not intend to use a proprietary name for "Topotecan Injection".

2. Teva Parenteral Medicines, Inc. Site of Drug Product Manufacture
19 Hughes
Irvine, CA 92618-1902

Teva Pharmaceuticals USA Inc. Site of Drug Product Distribution
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Cory

From: Varney, Deanne [mailto:Deanne.Varney@fda.hhs.gov]
Sent: Wednesday, November 07, 2012 3:00 PM
To: Philip Erickson; FDA SharedMailbox
Subject: NDA 22453

Hello Dr. Erickson,

Please provide responses to the below questions regarding NDA 22453 (topotecan) by COB on Thursday, November 8, 2012.

1. Does TEVA intend for “Topotecan Injection” to be a proprietary name? If so, has a proprietary name request been submitted?
2. Please clarify what entity is manufacturing the product and what entity is distributing the product.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
11/13/2012

TEAM MEETING #2 MINUTES
October 3, 2012

505(b)(2) NDA 22453 (Class 2 Resubmission)
Topotecan Hydrochloride Injection, 1 mg base/mL
Teva Pharmacueticals USA

Purpose: Response to October 16, 2009 CR letter. Provides additional CMC information to resolve cGMP-related issues, final labeling, and a safety update. All other disciplines previously determined application to be approvable.

Teva is relying on GlaxoSmithKline's Hycamtin® as the previously approved drug under NDA 20-671. The reference listed drug is manufactured as a lyophilized powder and is available in 4 mg single-dose vials. Teva's proposed drug product will be supplied as an injectable solution containing 1 mg base/mL; 4 mL fill in a 6 mL vial.

Application Receipt Date: June 25, 2012

Review Team:
Deanne Varney, Regulatory Project Manager
Shakun Malik, Medical Officer/Clinical Reviewer
John Johnson, CDTL
Dubravka Kufrin, Nonclinical Reviewer
Ruby Leong, Clinical Pharmacology Reviewer
Debasis Ghosh, Quality Reviewer
Elsbeth Chikhale, Biopharmaceutics Reviewer
Denise Miller, Microbiology Reviewer
Carole Broadnax, DPDP Reviewer
Karen Munoz, DCDP Reviewer

Agenda Items:

1. **Review Upcoming Dates/Milestone**:

   - **Goal Date**: 12/14/2012

2. **Review Status**
   - CMC: Extensive revisions were made that require a CMC review. CMC has determined that a pharm/tox review is not required. The review is still in progress, with a draft anticipated on 10/12/2012.
   - Biopharmaceutics: Biowaiver granted; approvable (8/31/2012)
   - Pharm/Tox: No review required. One sentence memo will suffice.
   - Clinical: One sentence memo uploaded in DARRTS on 9/27/12

- Clin/Pharm: One sentence memo uploaded in DARRTS on 10/3/2012
- Facility: All sites expected to be acceptable, final determination will be made after CMC review.

3. **Required Consults**

- EER – EES acceptable (8/31/2012)
- Microbiology – Consult sent on 7/5/2012
- OPDP – Consult sent on 9/20/2012
- OSE – Consult sent on 9/20/2012

4. **Labeling Meetings:**

Labeling Meeting #1 to discuss PI: 11/5/2012
Labeling Meeting #2 to discuss carton/container: 11/7/2012
Labeling Meeting #3 if needed: 11/29/2012

5. **PI:** Labeling negotiations occurred during the first review cycle in 2009. However, due to changes in the RLD labeling, the version the sponsor has included in the resubmission is significantly different than the version agreed upon in 2009.

6. **Review Plan/Action Items**

- CMC will review the 2009 agreed-upon PI and determine if all FDA comments are incorporated, in principle, in the currently proposed PI

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DEANNE R VARNEY
10/03/2012

From:	Mesmer, Deborah
To:	"Philip Erickson"
Cc:	Varney, Deanne
Subject:	NDA 022453- Information request dated 10/1/12
Date:	Monday, October 01, 2012 3:10:31 PM

Dear Mr. Erickson,

Please refer to NDA 022453 for Topotecan Injection, 1 mg base/mL. We have the following comments and requests for information:

1) The endotoxin testing method has been revised to include a possible pH adjustment if the product's test dilution (b) (4) is outside the manufacturers recommended pH range. The SOP revision was effective in May 2011. The Enhancement/Inhibition testing for this drug product was performed in 2008. There was no information provided as to whether or not this change in the SOP impacts the endotoxin testing of the drug product. Provide an updated Enhancement/Inhibition report or justify how the 2008 report remains valid.

2) The endotoxin reduction validation for the (b) (4) stoppers was not found in the submission nor was there a reference to a DMF. Provide either the validation study or a reference to a DMF for the endotoxin reduction studies for stoppers received from the manufacturer of the (b) (4) stoppers.

Please provide your response no later than October 12, 2012. Please acknowledge receipt of this message, and let me know if you have any questions.

Sincerely,

Deborah Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 1627
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
10/01/2012

From:	Mesmer, Deborah
To:	"Philip.Erickson@tevapharm.com"
Cc:	Varney, Deanne
Subject:	RE: NDA 22453 - DMF correspondence
Date:	Wednesday, September 26, 2012 7:22:14 AM

Dear Mr. Erickson,

Please refer to NDA 022453 for Topotecan Injection, 1 mg base/mL. We have the following comment and request for information. Please submit your response to your application no later than September 28, 2012.

> The drug substance information provided in Sec 2.3.S.1 and 3.2.S.1 are not consistent with the information available in the current Type II DMF (b) (4). Based on the information provided in the current DMF (b) (4), we recommend that you update the above sections to reflect those changes.

Please acknowledge receipt of this message, and let me know if you have any questions.

Sincerely,

Deborah Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 1627
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
09/26/2012

From:	Mesmer, Deborah
To:	"Philip.Erickson@tevapharm.com"
Cc:	Varney, Deanne
Subject:	NDA 22453 - DMF correspondence
Date:	Thursday, September 13, 2012 11:40:09 AM

Dear Mr. Erickson,

Please refer to NDA 022453 for Topotecan Injection, 1 mg base/mL. We have the following comment:

A letter dated September 12, 2012, requesting information has been issued to the designated agent for DMF (b) (4)

Please acknowledge receipt of this message.

Sincerely,

Deborah Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 1627
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-4023
deborah.mesmer@fda.hhs.gov

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/s/

DEBORAH M MESMER
09/13/2012

TEAM MEETING #1 MINUTES
September 5, 2012

505(b)(2) NDA 22453 (Class 2 Resubmission)
Topotecan Hydrochloride Injection, 1 mg base/mL
Teva Pharmacueticals USA

Purpose: Response to October 16, 2009 CR letter. Provides additional CMC information to resolve cGMP-related issues, final labeling, and a safety update. All other disciplines previously determined application to be approvable.

Teva is relying on GlaxoSmithKline's Hycamtin® as the previously approved drug under NDA 20-671. The reference listed drug is manufactured as a lyophilized powder and is available in 4 mg single-dose vials. Teva's proposed drug product will be supplied as an injectable solution containing 1 mg base/mL; 4 mL fill in a 6 mL vial.

Application Receipt Date: June 25, 2012

Review Team:
Deanne Varney, Regulatory Project Manager
Shakun Malik, Medical Officer/Clinical Reviewer
John Johnson, CDTL
Dubravka Kufrin, Nonclinical Reviewer
Ruby Leong, Clinical Pharmacology Reviewer
Debasis Ghosh, Quality Reviewer
Elsbeth Chikhale, Biopharmaceutics Reviewer
Denise Miller, Microbiology Reviewer
Carole Broadnax, DPDP Reviewer
Karen Munoz, DCDP Reviewer

Agenda Items:

1. **Review Upcoming Dates/Milestone**:

   - **Goal Date**: 12/25/2012 (6-month clock) --- moved to **12/14/2012**

2. **Review Status**

   - CMC: Extensive revisions were made that require a CMC review. CMC has just received the DMF, therefore there are no updates to report at this time. CMC will confirm if a pharm/tox review will be needed by 9/26/2012.

- Biopharmaceutics: Biowaiver granted; approvable (8/31/2012)

- Pharm/Tox: Necessity for a pharm/tox review to be determined by CMC

- Clinical: One sentence memo will suffice

- Clin/Pharm: One sentence memo will suffice

- Facility: All sites expected to be acceptable. Final determination will occur following the CMC review.

3. **Required Consults**

    - EER – EES acceptable (8/31/2012)
    - Microbiology – Consult sent on 7/5/2012

4. **Labeling Meetings:** Two labeling meetings are needed: one to discuss the Carton and one to discuss the PI

5. **Review Plan/Action Items**

    - CMC will conduct a review of the resubmission, and will determine by 9/26/12 if a P/T review is needed
    - RPM to obtain all approved topotecan labels

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/s/

DEANNE R VARNEY
09/06/2012

PLANNING MEETING MINUTES
July 18, 2012

505(b)(2) NDA 22453 (Class 2 Resubmission)
Topotecan Hydrochloride Injection, 1 mg base/mL
Teva Pharmacueticals USA

Purpose: Response to October 16, 2009 CR letter. Provides additional CMC information to resolve cGMP-related issues, final labeling, and a safety update. All other disciplines previously determined application to be approvable.

Teva is relying on GlaxoSmithKline's Hycamtin® as the previously approved drug under NDA 20-671. The reference listed drug is manufactured as a lyophilized powder and is available in 4 mg single-dose vials. Teva's proposed drug product will be supplied as an injectable solution containing 1 mg base/mL; 4 mL fill in a 6 mL vial.

Application Receipt Date: June 25, 2012

Review Team:
Deanne Varney, Regulatory Project Manager
Shakun Malik, Medical Officer/Clinical Reviewer
John Johnson, CDTL
Dubravka Kufrin, Nonclinical Reviewer
Ruby Leong, Clinical Pharmacology Reviewer
Jean Tang, Quality Reviewer
Carole Broadnax, DPDP Reviewer
Karen Munoz, DCDP Reviewer

Agenda Items:

1. **Review Upcoming Dates/Milestone**:

   - **Goal Date**: 12/25/2012 (6-month clock)

2. **Review Status**
   - CMC: Extensive revisions were made that require a CMC review. CMC will confirm if a pharm/tox review will be needed and if the previously granted biowaiver still holds.
   - Pharm/Tox: Necessity for a pharm/tox review to be determined by CMC
   - Clinical: One sentence memo will suffice
   - Clin/Pharm: One sentence memo will suffice
   - Facility:

i. Teva Irvine facility is currently unacceptable due to a violative inspection in 2010 and a violative follow-up inspection in 2012 that maintained the OAI status.

ii. (b) (4) facility was inspected in (b) (4) and the team is recommending a warning letter. A request for additional information (RAI) letter was sent to the facility in (b) (4) and the response was just received and is under review.

3. **Required Consults**

- EER – Facilities already entered into EES
- Microbiology – Consult sent on 7/5/2012

4. **Labeling Meetings:** No labeling meetings required

5. **Review Plan/Action Items**

- CMC will conduct a review of the resubmission
- CMC will confirm if a pharm/tox review is required
- CMC will determine if the previously granted biowaiver still holds
- Will hold early team meetings with CMC and Facilities

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/s/

DEANNE R VARNEY
07/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22453

ACKNOWLEDGE – CLASS 2 RESPONSE

Teva Pharmaceuticals, USA
Attention: Philip Erickson, R.Ph.
Vice President, Regulatory Affairs
1090 Horsham Road
PO Box 1090
North Wales, PA 19454

Dear Dr. Erickson:

We acknowledge receipt on June 25, 2012, of your June 22, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topotecan Injection, 1 mg base/mL.

This resubmission contains updated chemistry, manufacturing, and controls (CMC) information; updated labeling; and a safety update, submitted in response to our October 16, 2009 complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is December 25, 2012.

If you have any questions, call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
07/05/2012

Jamison, Janet

From: Jamison, Janet
Sent: Thursday, August 27, 2009 7:01 AM
To: 'Susan.O'Brien@tevausa.com'
Subject: N22-453 FDA Response to 8-24-09 Draft Label

Attachments: draft-labeling-text-Teva 8-24 FDA 8-26-09.doc

Ms. O'Brien,

Your response to our labeling comments was received August 24,2009 and has been reviewed.

Attached is the FDA final label version with minor revisions.

draft-labeling-text-Teva 8-24 ...

Please acknowledge receipt. Please also respond to me by e-mail with your agreement/non-agreement along with justification by the end of the day Friday, August 28.

Let me know if you have questions or need further clarification.

Best regards,

Janet Jamison

From: Jamison, Janet
Sent: Wednesday, August 19, 2009 3:21 PM
To: 'Susan.O'Brien@tevausa.com'
Subject: N22-453 FDA Draft Label Review

Ms. Obrien,

In reference to your new drug application (NDA), submitted December 17, 2008, for Topotecan Injection, the review has been completed of the proposed package insert (labeling).

Attached is draft labeling with FDA comments in tracked changes for your review. << File: NDA 22453 proposed PI FDA Version 8-18-09.doc >>

We request your review and response by Tuesday August 25, noon. Please accept changes you are in agreement with; provide tracked changes/comments for those areas requiring further discussion and review.

Please acknowledge receipt.

Best regards,

Janet Jamison

Regulatory Project Manager
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2116
Silver Spring, MD 20993
301-796-2313
FAX 301-796-9845

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Jamison, Janet

From: Jamison, Janet
Sent: Wednesday, August 19, 2009 3:21 PM
To: 'Susan.O'Brien@tevausa.com'
Subject: N22-453 FDA Draft Label Review

Attachments: NDA 22453 proposed PI FDA Version 8-18-09.doc

Ms. Obrien,

In reference to your new drug application (NDA), submitted December 17, 2008, for Topotecan Injection, the review has been completed of the proposed package insert (labeling).

NDA 22453
oposed PI FDA Vers

Attached is draft labeling with FDA comments in tracked changes for your review.

We request your review and response by Tuesday August 25, noon. Please accept changes you are in agreement with; provide tracked changes/comments for those areas requiring further discussion and review.

Please acknowledge receipt.

Best regards,

Janet Jamison

Regulatory Project Manager
FDA/CDER/OODP/DDOP
10903 New Hampshire Avenue
Bldg. 22/Room 2116
Silver Spring, MD 20993
301-796-2313
FAX 301-796-9845
E-Mail: janet.jamison@fda.hhs.gov

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/s/

JANET K JAMISON
08/20/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-453

INFORMATION REQUEST

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618

Dear Ms. O'Brien:

Please refer to your new drug application (NDA) dated December 17, 2008, received December 18, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Topotecan Hydrochloride Injection, 1 mg base/vial.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following information request. We request a written response within 7 days of the date of this letter in order to continue our evaluation of your NDA:

The provided stability data package does not support a commercially viable expiration dating period. Provide 9-month and 12-month stability data for the drug product.

If you have any questions, call Deborah Mesmer, Regulatory Project Manager, at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope Miksinski
08/12/2009

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Susan O'Brien**	**From:**	**Susan Jenney, MS**
FAX:	**949-583-7351**	**FAX:**	**301-796-9845**
E-mail:	**Susan.O'Brien@tevausa.com**	**E-mail:**	**Susan.Jenney@fda.hhs.gov**
Phone:	**949-455-4724**	**Phone:**	**301-796-0062**
Pages, including cover sheet: 4		**Date:**	**July 10, 2009**

RE: Information Requests for NDA 22-453

Dear Ms. O'Brien:

Please refer to your New Drug Application (NDA 22-453) for Topotecan Injection submitted on December 17, 2008. During our review of the Chemistry section of your submission, we have the following Information Requests:

Deficiencies

1. Drug Master File (DMF) (b) (4) for the drug substance topotecan hydrochloride was found to be deficient. The DMF holder has been notified of the deficiencies on July 7, 2009. The NDA can not be approved without a satisfactory response to the DMF deficiencies.

2. The following comments pertain to Section 3.2.P.2.6, In-use study:
   (a) You state on page 8 of this report that "topotecan impurity profiles remained the same for all (b) (4) stored at ambient room temperature and ambient lighting conditions." Provide data for impurity profiles.
   (b) It is stated on page 9 that (b) (4) was not detected. Provide analytical method for (b) (4) analysis and other possible leachables.

3. You state in Section 3.2.P.3.4 that the exhibit stability lots of the drug product met all proposed in-process bulk solution test specifications. However, the bulk solution testing results as shown in Tables 3.2.P.4-2 and 2.3.P.3.1 do not appear to meet your proposed in-process acceptance criteria for osmolality, pH, and assay. Inconsistencies are also noted between the proposed in-process specification in the above tables and the specification listed in the production batch records for bulk lot numbers 31302593, 31302594, and 31302595 (information provided in the same section). Please clarify.

4. Use appropriate decimal places for the acceptance criteria for impurities in the drug substance in accordance with ICH Q3A. For example, ICH Q3A specifies that two decimal places (e.g., 0.06 percent, 0.13 percent) be used for impurities below 1.0 percent. Therefore, revise the acceptance criterion for (b) (4) from the currently proposed (b) (4) in the drug substance specification. Revise the acceptance criteria for all other impurities accordingly.

5. Provide in sections 3.2.S.5 and 3.2.P.6 the batch number, synthesis, characterization, and certificate of analysis for the reference standards of impurities (e.g., (b) (4)) that are used in the testing of the drug substance and drug product.

6. It appears that the acceptance criteria for higher and lower fill volumes are reversed in Tables 2.3.P.3-3 and 3.2.P.3.4-3. Therefore, revise these two tables with correct fill volume limits and results. Also note comment 7(b) below for the required fill volume.

7. The following comments pertain to the drug product specification in Tables 2.3.P.5-1 and 3.2.P.5.1-1:
   (a) Your specification table, which only includes columns for tests and acceptance criteria, is inadequate. Note that a specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, according to ICHQ6A. Therefore, revise the specification table to add a column for references to analytical procedures. For the analytical procedures that conform to USP general procedures, provide USP general procedure numbers along with Teva's reference numbers.
   (b) The acceptance criterion for the fill volume (NMT (b) (4)) is not acceptable. Injections are required to be filled with a volume in slight excess of the labeled volume to permit withdrawal of the labeled amount (refer to USP <1151>). Therefore, revise the acceptance criterion for the fill volume to meet the USP requirements.

8. Provide a drug substance specification table in section 3.2.S.4.1 including tests, references to analytical procedures, and appropriate acceptance criteria. Refer to comment 7(a) above.

9. Inconsistencies have been noted regarding packaging presentations. The "How Supplied" section of the package insert includes only one packaging presentation (1 vial in a carton). However, Section 3.2.P.7 (Container Closure System) of the NDA includes additional packaging (five single-dose vials contained within a carton). Clarify and revise the sections accordingly.

10. The following comments pertain to the immediate container label:
    (a) Revise the drug name from (b) (4) to "Topotecan Injection." The strength of the drug product (1 mg /mL) is based on the topotecan free base. The established name of the drug product and the declared strength should match. Refer to USP <1121> Nomenclature for the naming policy for the drug products formulated with a salt.
    (b) Injectable drug products should be labeled primarily in terms of total amount (with prominent expression in bold characters), followed immediately by contents per mL enclosed by parentheses. Refer to USP <1> Injections. Therefore, revise the presentation of the strength and content from the current "1 mg base/mL" to the following:

        4 mg/4 mL
        (1 mg/mL)

    (c) Add the following statement immediately beneath the strength: "Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base."
    (d) Add "Must be diluted before use" immediately beneath "For Intravenous Use."

11. The following comments pertain to the carton labeling:
    (a) Comments (a) through (d) for container labels, as listed above, also apply to carton labeling. Revise the carton labeling accordingly.
    (b) Display "Rx only" prominently on the main panel.
    (c) It is recommended that the labeling contains a statement of being sterile.

12. The following comments pertain to SPL Drug Listing Data Element (DLDE):
    (a) Change the drug name from [redacted] (b) (4) to "Topotecan Injection" and replace [redacted] (b) (4) with "topotecan injection, solution."
    (b) Inconsistencies have been noted regarding packaging presentations. The "How Supplied" section of the package insert only provides a NDC number for 1 vial in a carton, but the SPL Drug Listing Data Element (DLDE) indicates that there are 2 NDC numbers, each for 1 vial and 5 vials respectively in a carton. Clarify the information regarding packaging presentations and revise the package insert, DLDE, carton labeling, and the container information in Section 3.2.P.7 and 2.3.P.7 accordingly.

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

In order for us to complete our review, please respond to these requests by no later than July 24, 2009. Please submit an amendment to your application with your response to the deficiencies using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Susan.Jenney@fda.hhs.gov) or FAX (301-796-9845).

Thank you,
Susan Jenney, MS
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Drug Oncology Products
FDA/CDER/OND

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/s/

Susan Jenney
7/10/2009 10:29:28 AM

From: Jenney, Susan
Sent: Tuesday, July 07, 2009 4:26 PM
To: Greeley, George
Cc: Stowe, Ginneh D.; Jamison, Janet
Subject: RE: NDA 22-453 Topotecan Hydrochloride

Thank you, George!

From: Greeley, George
Sent: Tuesday, July 07, 2009 4:23 PM
To: Jenney, Susan
Cc: Stowe, Ginneh D.
Subject: NDA 22-453 Topotecan Hydrochloride
Importance: High

Hi Susan,

The Topotecan Hydrochloride full waiver was reviewed by the PeRC PREA Subcommittee on June 24, 2009. The Division recommended a full waiver because necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

Pre-NDA meeting

MEETING MINUTES

MEETING/TELECON DATE: November 14, 2008 **TIME:** 3-4 PM
LOCATION: FDA, White Oak Building 22, Conference Room 2201

IND/NDA: IND 103440 **Meeting Request Submission Date:** September 3, 2008
Briefing Document Submission Date: September 3, 2008

DRUG: Topetecan Hydrochloride Injection

SPONSOR/APPLICANT: Teva Parenteral Medicines, Inc.

TYPE of MEETING: To discuss the proposed NDA for Topetecan Hydrochloride Injection.

FDA PARTICIPANTS:
Robert Justice, M.D., Director, OODP
Sarah Pope, Ph.D., Acting Branch Chief, ONDQA/DPAMS/Branch 5
Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Jila H Boal, Ph.D., CMC Reviewer
Jian Wang, Ph.D., Clinical Pharmacology Reviewer
Julie Bullock, Pharm.D., Acting Team Leader, Office of
Clinical Pharmacology, Division of Clinical Pharmacology
Michael Brave, M.D., Medical Reviewer
Margaret Brower, Ph.D., Toxicology and Pharmacology Reviewer;
Haleh Saber, Ph.D., Acting Team Leader, Pharmacology/Toxicology
Capt Frank Cross Jr, M.A., M.T. (ASCP), Chief, Project Management Staff
Alberta E. Davis-Warren, B.S., Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Allyn Becker, Ph.D., Sr. Director, R&D
Sunni Churchill, Manager, Regulatory Affairs
Gregg DeRosa, Sr. Director, Biopharmaceutics
Jiin Felgner, Ph.D., Principal Scientist, R&D
Michael Kosiec, Associate Director, Stability, R&D
Dr. Charles Lambert, Ph.D., DABT, Toxicology Consultant
Susan O'Brien, Director, Regulatory Affairs
Elizabeth Rody, Clinical Research Scientist

BACKGROUND: Sponsor is using IND 103440 to investigate treatment of (b) (4) carcinoma of the ovary after failure of initial or subsequent chemotherapy, and small cell lung cancer sensitive disease after failure of first-line chemotherapy. Also, Topotecan Hydrochloride Injection in combination with cisplatin is indicated for the treatment of: stage IV - B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery

and/or radiation therapy. The sponsor submitted a meeting request on September 3, 2008 to discuss the proposed NDA for Topetecan Hydrochloride Injection. The sponsor submitted a subsequent background package on September 3, 2008. FDA sent the sponsor preliminary responses on November 13, 2008 by fax in order to facilitate the meeting.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Pre-Clinical

1) Teva's proposed drug product is pharmaceutically equivalent to Hycamtin® manufactured by GlaxoSmithKline. Teva's proposed drug product formulation is a liquid formulation and is identical to the GlaxoSmithKline's Hycamtin® upon reconstitution with the exception of the pH. The pH of Teva's formulation is 2.2 as compared to 3.0 for reconstituted Hycamtin® for better physical chemical stability of the liquid formulation. Our proposed drug product has the same route of administration and is intended for the same indication as that of Hycamtin®. Therefore, in accordance with Section 505(b)(2) of the Act, Teva does not intend to conduct toxicological studies, since we may rely on the Agency's prior finding of safety for Hycamtin®. Does the agency agree that the toxicological studies are not necessary?

   FDA response: You have indicated that (b) (4) has been studied pre-clinically in rodents, and clinically at a dose of (b) (4) for 5 days. Please provide these data in order to justify the (b) (4) limit of (b) (4)

   Meeting Discussion: The sponsor gave a presentation (see attached) to support their position and will provide these data with the NDA.

Clinical

2) Teva's proposed drug product is pharmaceutically equivalent to Hycamtin®, manufactured by GlaxoSmithKline. Teva's proposed drug product formulation is a liquid formulation and is identical to the GlaxoSmithKline's Hycamtin® upon reconstitution with the exception of the pH. The pH of Teva's formulation is 2.2 as compared to 3.0 for reconstituted Hycamtin® for better physical chemical stability of the liquid formulation. Our proposed drug product has the same route of administration and is intended for the same indication as that of Hycamtin®. Therefore, in accordance with Section 505(b)(2) of the Act, Teva does not intend to conduct clinical studies, since we may rely on the Agency's prior finding of efficacy for Hycamtin®. Does the agency agree that the clinical studies are not necessary?

   FDA response: Yes.

3) Teva's proposed drug product is a parenteral solution intended solely for administration by injection, and contains the same active ingredient as that of GlaxoSmithKline's Hycamtin®, the subject of an approved new drug application. Additionally, our proposed

drug product has the same inactive ingredients in the same concentration as that Hycamtin®. Furthermore, our drug product is intended for the same indication as that of Hycamtin®. We would like to confirm Agency agreement that a bioequivalence study can be waived, in accordance with 21 CFR §320.22(b)(1)(i) and (ii).

FDA response: Yes.

Chemistry, Manufacturing and Controls (CMC)

4) Teva has established specifications for our drug substance based on the ICH guidance document *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances (Q6A), Impurities in New Drug Substances Q3A(R)and Impurities in New Drug Products Q3B(R).* Does the Agency agree with Teva's proposed specifications as provided in Module 3.2.S.4.1 Drug Substance Specifications Table 3.2.S.4.1-1?

FDA Response:
The final acceptability of your proposed drug substance specifications will be determined during NDA review. Also see the following comments:

- **Include a side-by-side comparison of three batches of listed drug substance close to expiry with three batches of the proposed drug substance, as generated using your proposed analytical methods. If the comparison indicates any significant difference in impurity profile and if any impurities exceed ICH Q3B(R2) in your product, then those impurities will need to be adequately qualified. Additionally, clearly identify all chemical structures exceeding the identity threshold.**

- **DMF (b) (4) will be reviewed at the time of NDA submission, with respect to the manufacturing process and process controls.**

- **The water content of the drug substance (with an acceptance criteria of (b) (4) suggests that the drug substance is a (b) (4). Provide the hydration state of the drug substance.**

- **Justify your proposed storage conditions, as the drug substance appears to be light-sensitive.**

Meeting Discussion: Sponsor stated that it would be difficult to obtain API from the RLD supplier. The agency acknowledged and suggested that the sponsor provide any additional information on impurity profiles of drug substance and drug product. Sponsor confirmed that they would follow ICHQ3A guidelines for the drug substance specifications. FDA confirmed that the overall acceptability of the impurity profile of the drug substance is a review issue.

The sponsor will consult the DMF holder regarding the issue of drug substance hydration. This information will be provided with the NDA.

5) Teva has established specifications for our drug product based on the ICH guidance document *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances (Q6A), Impurities in New Drug Substances Q3A(R)and Impurities in New Drug Products Q3B(R)* and a toxicological evaluation of [redacted] (b) (4). Does the Agency agree with our proposed specifications as provided in Module 3.2.P.5.1 Drug Product Specifications Table 3.2.P.5.1-1?

FDA response:
The final acceptability of your proposed drug product specifications will be determined during NDA review. Also note the following comments:

- **We do not expect that Teva's product be identical to the reference listed drug with regard to components and composition or the dosage form. However, clearly describe any differences in the components and/or composition and provide a scientific rationale that indicates that such differences do not contribute to large variations in the formulation. Therefore, provide adequate information on your formulation development and justify why any formulation differences are not likely to affect the drug product quality and performance. Also, provide comparative batch analysis data between the proposed formulation and the reference listed product (close to the expiry) to confirm similar impurity profiles, and justify why additional safety qualification studies are not needed.**

- **Since the drug product is photosensitive, we recommend that you store the drug product in an amber glass vial. Alternatively, place the statement "Protection from light" on the label.**

- **The photodegradation products in the drug product that exceed the ICH Q3B identification and qualification thresholds need to be specified, identified, and qualified with appropriate acceptance criteria.**

- **Provide compatibility data for the formulation and the stopper under stressed storage conditions to identify potential leachables.**

- **Identify and propose corresponding acceptance criteria for any potential leachables in the drug product that exceed the Concerned Critical Toxicological Thresholds (CCTT).**

- **Propose a specification for fill volume in your stability program.**

- **Include Container Closure Integrity (CCI) testing in your release and stability specifications.**

- **(b) (4) the vial head space (4 ml fill in a 6 ml vial) (b) (4) or provide justification that this is not needed.**

Meeting Discussion: Regarding the first bullet, the sponsor stated that the RLD batch being used for comparison is approximately twenty-two months prior to expiry. The Agency responded that ideally, a batch that was closer to its expiry would be used. Sponsor confirmed that the stability studies will include parallel testing of the RLD batch and the proposed commercial formulation, and that full stability information will be submitted in the original NDA.

6) Teva has placed three exhibit batches of Topotecan Hydrochloride Injection into the stability program at 5°C, 25°C, 30°C, and 40°C to support a 24 month shelf-life at a storage condition of 2-25°C. Does the Agency agree that the current stability data and toxicological evaluation as provided in the information package (3.2.P.5) supports a 24 month shelf-life at a storage condition of 2-25°C?

FDA response:
The acceptability of your drug product expiration dating period is a review issue and will depend on the adequacy of the stability results and the amount of the drug product stability data provided at the time of NDA submission. Also note the following comments:

The storage condition of 2-(b) (4)C appears to be very broad. According to the data provided in your meeting package, the more favorable long-term storage condition is (b) (4)C for the drug product, protected from light. In your NDA, a single temperature for long term storage needs to be selected. Note that the acceptability of the stability data also depends on six months of satisfactory accelerated stability data for the chosen storage conditions.

The acceptance criteria of NMT (b) (4)% for (b) (4) in the drug product is acceptable provided that the Pharmacology-Toxicology team concur with your qualification assessments and toxicity data. We refer you to the response to Question 1 above.

Regulatory

7) Our proposed drug product does not contain a new active ingredient, and is not for a new indication, new dosing regimen, nor a new route of administration. Therefore, in accordance with 21 CFR §314.55(a) a pediatric assessment is not required. Does the Agency agree that an assessment is not required?

FDA response: Your NDA should include your waiver request which will then be reviewed by PeRC.

Meeting Discussion: The sponsor will submit the waiver request with the NDA.

Additional CMC Comments to the Applicant:

- **Provide a comparison of the intended drug product commercial batch size vs the batch size used for the exhibit batches.**

- **Provide compatibility studies between the drug product and the proposed diluents (0.9% Sodium Chloride Injection and 5% Dextrose Injection) in the NDA. Reference to the NDA for the lyophilized product is considered as supportive data.**

ACTION ITEMS:

1. None

Alberta Davis-Warren
Project Manager

Concurrence Chair: Dr. Sarah Pope

Attachments: Overheads not in briefing document

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Linked Applications	Sponsor Name	Drug Name / Subject
IND 103440	TEVA PARENTERAL MEDICINES INC	TOPOTECAN HYDROCHLORIDE INJECTION

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/s/

SARAH C POPE
01/07/2009

Jenney, Susan

From: Jenney, Susan
Sent: Wednesday, May 20, 2009 6:12 PM
To: Susan.O'Brien@tevausa.com
Cc: 'Sunni.Churchill@tevausa.com'; Jenney, Susan
Subject: 22-453 Topotecan - Information request

Good afternoon:

Please refer to your NDA 22-453 (topotecan) submitted on December 17, 2008. During the review or your submission, the Microbiologist Reviewer has the following information request:

1. Please provide the (b) (4) validation report. It appears to be missing from section 3.2.P.3.5.2.

Contact me if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

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/s/

Susan Jenney

5/20/2009 06:17:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-453

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618

Dear Ms. O'Brien:

Please refer to your new drug application (NDA) dated December 17, 2008, received December 18, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Topotecan Hydrochloride Injection, 1 mg base/vial.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 18, 2009.

During our filing review of your application, we identified the following potential review issues:

1. Six months of stability data is not adequate (in terms of duration) to support the proposed drug product shelf-life of 24-months. Based on the data provided, the maximum possible shelf-life that may be considered based on this paucity of data is 12 months if all of the data (6 months long-term and 6 months accelerated) are acceptable.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. The labeling does not provide instructions for handling the product after dilution for intravenous administration. Improper or prolonged storage prior to administration may permit the growth of inadvertent microbial contamination that may occur during the dilution procedure and therefore affects patient safety. Reference is made to *Guidance for*

Industry: ICH Q8 Pharmaceutical Development, Section II.E and *Guidance for Industry*: *ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7.

2. The label should provide a time limit and storage conditions for the product after dilution into the IV fluid. It is recommended that the post-dilution storage period is not more than 4 hours at room temperature or not more than 12 hours at refrigerated temperature. If the label's storage limit exceeds these times, then those limits should be supported by a risk assessment that includes studies designed to detect growth of adventitious microbial contamination under the recommended storage conditions.

3. If a study is performed, then the report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the counts increase more than 0.5 Log_{10} (based on the statistical sensitivity of the assay), or when trended data indicate initiation of growth. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended diluting fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. The USP <51> is quoted as a reference of the organisms to be used and not for the test procedure or acceptance criteria described in the chapter.

<u>Issues concerning your package insert:</u>
HIGHLIGHTS OF PERSCRIBING INFORMATION:

4. The summarized statements need to refer to a section in the full prescribing information in the format (X.X).
5. White space is needed between each major section.
6. Add the BOXED WARNING and summarize the warnings.
7. "**See full prescribing information for complete boxed warning**" must be placed immediately following the heading of the BOXED WARNING.
8. "Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus." is not included under WARNINGS AND PRECAUTIONS and should reference (5.X) and (8.1).
9. Add a major section for PATIENT COUNSELING INFROMATION and add the statement "**See 17 for PATIENT COUNSELING INFORMATION.**"

PERSCRIBING INFORMATION: CONTENTS:

10. Add the BOXED WARNING title to the beginning of the table of contents in upper case, bolded letters.
11. Line up 1.1 to line up with the rest of the subheadings.
12. Change 1.3 to 1.2. Subsection 1.3 does not exist in the full prescribing information.
13. Change the title "General" for subsection 5.1 to identify the content of the subsection.
14. Change the subheading numbers for the CLINICAL PHARMACOLOGY to match the sections in the Full Prescribing Information.

15. Add a horizontal line between the Table of Contents and the Full Prescribing Information.

FULL PRESCRIBING INFORMATION:

16. Change the references throughout the Full Prescribing information in the format: *[see Section Title (X.X)]*. For example *[see Indications and Usage (1.1)]*. Note the formatting used in the reference.
17. Add the subject of the warning in your BOXED WARNING. This will also be the title for the HIGHLIGHTS and TABLE OF CONTENTS. For example: WARNING: SUBJECT OF WARNING.
18. Bold all the words contained in your BOXED WARNING and include a cross reference to more detailed discussion in other sections.
19. Add an "S" after the word "FORM" in the title of section 3.
20. Add the statement under DOSAGE AND ADMINISTRATION: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"
21. Change the title for section 5.1 to reflect the true contents of the subsection.
22. Change the title for subsection 5.2 to match the title in the Table of Contents.
23. Add a subsection under WARNINGS AND PRECAUTIONS for Pregnancy and add the statement "(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Briefly describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus." Cross reference to subsection (8.1).
24. Change the nonspecific terms from the ADVERSE REACTIONS section according to Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (http://www.fda.gov/cder/guidance/5537fnl.htm).
25. Reword the title to Table 7 to not use promotional words such as "Improvement."
26. For Table 7, center the column for CAV (%) to be consistent with the rest of the table.
27. Add the manufacturer information at the end of the label.

Issues concerning your carton and container labels:

28. It is noted that only labeling text is submitted for the container label and carton labeling. Therefore, submit container label and carton labeling in color mock-up format that is proposed for marketed product.

If you have not already done so, you must 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. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We note that your proposed **Highlights** of Prescribing Information is more than one-half page. We will review this during labeling discussions.

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 because the disease is typically in adults and has not shown a benefit in the pediatric population.

If you have any questions, call Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Division Director
Division of Drug Oncology Products
Office of Drug Oncology Products
Center of Drug Evaluation and Research

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/s/

Alice Kacuba
2/27/2009 12:33:01 PM
Signing for Dr. Justice.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-453

NDA ACKNOWLEDGMENT

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618

Dear Ms. O'Brien:

Please refer to your new drug application (NDA) dated December 17, 2008, received December 18, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for.

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Topotecan Hydrochloride Injection, 1 mg base/vial

Date of Application: December 17, 2008

Date of Receipt: December 18, 2008

Our Reference Number: NDA 22-453

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 February 16, 2009, 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

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 me at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center of Drug Evaluation and Research

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/s/

Susan Jenney

1/7/2009 10:15:39 AM