

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-671/S-004

ADMINISTRATIVE DOCUMENTS

Acting Division Director Comments on sNDA

NDA: 20-671/004 (SE-1)

Applicant: SmithKline Beecham Pharmaceuticals

Drug: Hycamtin™ (topotecan HCl) Injection

Date: November 27, 1998

Background:

This efficacy supplement seeks approval of a new indication for the use of Hycamtin in the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy. The application is based on a single randomized trial (study 090) and three supportive single arm trials (studies 014, 053, and 092). Study 090 was a multicenter, comparative trial in 211 patients with sensitive small cell lung cancer who had relapsed at least sixty days after first-line chemotherapy. Patients were randomized to treatment with single agent topotecan or to the combination of cyclophosphamide, doxorubicin, and vincristine (CAV). The primary efficacy endpoints were response rate and response duration.

In study 090, the overall objective response rate (CR + PR) was 24% for topotecan vs. 18% for CAV. The difference in overall response rates (topotecan - CAV) was 6% (95% C.I.: -6 to 18%). The response duration was 14.4 weeks for topotecan vs. 15.3 weeks for CAV. The median time to progression was 13.3 weeks for topotecan and 12.3 weeks for CAV, and the hazard ratio for progression (topotecan:CAV) was 0.92 (95% C.I. 0.69 to 1.22). The median survival was 25.0 weeks for topotecan and 24.7 weeks for CAV, and the hazard ratio for death was 1.04 (95% C.I. 0.78 to 1.39). Nine disease-related symptoms were also assessed in this unblinded trial (Table 3). Each symptom was rated on a 4 point scale at baseline and before each visit. Improvement was defined as a one point improvement from baseline that was sustained over two courses. As is shown in the table below, a higher percentage of patients on the topotecan arm reported improvement in eight of the nine symptoms. Because of issues raised in the medical and statistical reviews, formal statistical comparisons between the two arms is not appropriate.

Table 3. Percentage of Patients with Symptom Improvement*: *Hycamtin* versus CAV in Patients with Sensitive Small Cell Lung Cancer

Symptom	<i>Hycamtin</i> (n=107)		CAV (n=104)	
	n**	(%)	n* *	(%)
Shortness of Breath	68	(27.9)	61	(6.6)
Interference with Daily Activity	67	(26.9)	63	(11.1)
Fatigue	70	(22.9)	65	(9.2)
Hoarseness	40	(32.5)	38	(13.2)
Cough	69	(24.6)	61	(14.8)
Insomnia	57	(33.3)	53	(18.9)
Anorexia	56	(32.1)	57	(15.8)
Chest Pain	44	(25.0)	41	(17.1)
Hemoptysis	15	(26.7)	12	(33.3)

* Defined as improvement sustained over at least two courses compared to baseline

**Number of patients with baseline and at least one post-baseline assessment

Topotecan patients experienced higher rates of grade 4 thrombocytopenia (29% vs. 5%) and grade 3 or 4 anemia (42% vs. 20%), but the rates of grade 4 neutropenia (70% vs. 71%) were similar on both arms. The number of courses with platelet transfusions (6% vs. 0.6%) and red cell transfusions (25% vs. 12 %) were higher for topotecan patients than for CAV patients. Non-hematologic toxicities were similar between the topotecan and CAV arms. The treatment-related death rate was 4.7% with topotecan and 3.8% with CAV.

Studies 014, 053, and 092 were multicenter trials of single agent topotecan in 319 patients with both sensitive and resistant relapsed small cell lung cancer. Sensitive was defined in these studies as responding to initial chemotherapy and progressing at least 90 days after the last treatment. In the 168 patients with sensitive disease, the objective response rates to topotecan ranged from 11% to 31%. These studies confirmed the activity of topotecan in the sensitive population and were supportive of Study 090.

On June 2, 1998, the supplemental new drug application was presented and discussed at the Oncologic Drugs Advisory Committee meeting. The Committee concluded that the response rate of 24 % in this setting with a duration of response of 14.4 weeks did provide substantial evidence of efficacy in the second-line treatment of patients with sensitive SCLC with support from the data on improvement in disease-related symptoms. After considering both the efficacy data and the incidence and severity of hematologic toxicity, the Committee recommended approval of topotecan for second-line treatment of sensitive small cell lung cancer.

Discussion of the Basis for Approval:

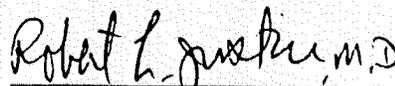
The results of treatment of recurrent small cell lung cancer with chemotherapy are poor and the intent of treatment is palliative. Unfortunately, there are no randomized controlled trials of CAV or other second-line chemotherapy in recurrent small cell lung cancer which can confirm the benefit of further treatment in this setting. Although the comparability of the populations is uncertain, median survivals reported in two studies of ineffective second-line therapy (none or cytarabine) were 1.5 to 2.5 months (Tummarello, et al. Anticancer Research 1990 and Albain, et al., Cancer 1993). The usual clinical practice in patients with sensitive disease is to utilize a combination regimen that is active in first-line treatment, either the same regimen that the patient responded to previously or a regimen that contains different drugs. Since the combination of etoposide and cisplatin is now commonly used as initial therapy (> 70% of patients on both arms had received it) and CAV is also highly active as first-line therapy, it is an appropriate control arm in this setting. While median survivals of 3.4 to 4.3 months have been reported for second-line therapy with CAV, the only evidence of efficacy in the literature that can be definitely attributed to therapy are the reported objective responses.

Based on their knowledge of and clinical experience with this disease, ODAC voted 8 to 1 in support of the statement that the response rate of 24% and median duration of response of 14 weeks with topotecan in this setting provided substantial evidence of efficacy in the second-line treatment of patients with sensitive small cell lung cancer. It is important to point out that the Committee was addressing this specific patient population and that its vote did not imply that similar response rates in other patient populations would provide substantial evidence of safety and efficacy. In response to Dr. Temple's question (minutes p. 270), the Committee also stated that the survival seen in both the topotecan and CAV arms was greater than would have been expected in an untreated population.

Objective responses and the Committee's clinical impression of a survival benefit, however, do not provide the sole basis for approval of this application. Study 090 also prospectively collected information on disease-related symptoms at baseline and before each visit. While the attempt to measure symptom improvement can be criticized because the assessments were unblinded, the data was incomplete, etc., the greater degree of improvement in symptoms with topotecan in 8 of the 9 symptoms, suggests that the benefit is likely to be real. The Committee concurred, voting 7 to 1 with 1 abstention, that the results of the disease-related symptom scale provided supportive evidence of the efficacy of topotecan in this setting. Finally, although the toxicities of both regimens were significant, the Committee voted 7 to 2 that topotecan should be approved for the second-line treatment of sensitive small cell lung cancer.

Recommended Regulatory Action:

The efficacy supplement should be approved.


Robert L. Justice, M.D.

cc:

Orig. NDA 20-671/S-004

HFD-150/Div. File

HFD-150/SHirschfeld

HFD-150/GWilliams

HFD-151/DCatterson

c:hycantin.doc

NDA 20-671
Hycamtin[®] (topotecan HCl)
Small Cell Lung Cancer Efficacy Supplement

Items 13/14: Patent Information

Pursuant to the provisions of 21 USC §355 (b) and 21 C.F.R. §314.53, particularly subsections (c) and (d), Applicant herewith submits the following patent information for each patent it believes it reasonably could assert against the manufacture, use or sale by another of certain compositions, formulations or uses of a drug or drug product for which Applicant is submitting this NDA:

- (i) Patent No. 5,004,758 expiring 2 April, 2008.
- (ii) Type of patent: drug, formulation and use.
- (iii) SmithKline Beecham Corp.
- (iv) The owner/applicant has a residence and is doing business in the United States.

SmithKline Beecham Pharmaceuticals declares that Patent No. 5,004,758 covers the composition (new chemical entity), a formulation, and a method of use of topotecan hydrochloride. This product is the subject of this application for which approval is being sought.

Memo Regarding Revisions to the Package Insert NDA 20671
Supplement for Second Line Therapy for Sensitive Small Cell Lung Cancer
Submission Date: December 5, 1997
July 23, 1998

The sponsor submitted draft labeling with the submission. Following the meeting of the Oncology Drug Products Advisory Committee on June 2, 1998, proposed changes to the package insert from the Division of Oncology Drug Products were submitted to the sponsor. The sponsor agreed to all the proposed changes with the exception of those noted below. In a memo dated July 6, additional changes were proposed. Following discussion with DDMAC in response to proposed marketing material, further changes are proposed for the Clinical Studies section above Table 3.

Previous wording:

Proposed wording:

The complete revised text is on the following pages. The Division accepts the package insert in its current version as accurately reflecting the data provided with the submission.

IS/

Steven Hirschfeld, MD, PhD
Medical Officer

ⁿ
IS/

Grant Williams, MD
Team Leader

MD
7/24/98

**Memo Regarding Revisions to the Package Insert NDA 20671
Supplement for Second Line Therapy for Sensitive Small Cell Lung Cancer
Submission Date: December 5, 1997
July 6, 1998**

The sponsor submitted draft labeling with the submission. Following the meeting of the Oncology Drug Products Advisory Committee on June 2, 1998, proposed changes to the package insert from the Division of Oncology Drug Products were submitted to the sponsor. The sponsor agreed to all the proposed changes with the exception of those noted below.

The following changes were made in Table 2 as a result of re-analysis of the data including previously missing data and were agreed upon by Dr. David Smith of the FDA and Dr. David Fitts of SmithKline Beecham.

The previous wording was :

The proposed wording is:

The complete revised text is on the following pages. The Division accepts the package insert in its current version as accurately reflecting the data provided with the submission.

7-8-98
Steven Hirschfeld, MD, PhD
Medical Officer

7-9-98
Grant Williams, MD
Team Leader

CC: ORIG. NDA 20-671
DIV FILE
HIRSCHFELD
DEATPERSON

EXCLUSIVITY SUMMARY for NDA # 20-671 SUPPL # 004 (SE1)

Trade Name HYCAMTIN™ FOR INJECTION Generic Name TOPOTECAN HCl

Applicant Name SMITHKLINE BEECHAM PHARMACEUTICALS HFD- 150

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES / ___ / NO / /

b) Is it an effectiveness supplement? YES / / NO / ___ /

If yes, what type? (SE1, SE2, etc.) SE1

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.

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

d) Did the applicant request exclusivity?

YES /___/ NO //

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO // OTC Switch /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 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# 20-671 TOPOTECAN HCl
NDA# _____
NDA# _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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:

YES / / NO / /

(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 /X/

(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 /X/

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:

Controlled trials 090 and supporting
studies 053, 014, 592

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:

090, 014, 053, 092 This NDA supplement

- 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 / <input checked="" type="checkbox"/> /	NO / <input type="checkbox"/> / Explain: _____
	:	_____
Investigation #2	:	
IND #	YES / <input checked="" type="checkbox"/> /	NO / <input type="checkbox"/> / 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 / <input type="checkbox"/> / Explain _____	:	NO / <input type="checkbox"/> / Explain _____
_____	:	_____
_____	:	_____
Investigation #2	:	
YES / <input type="checkbox"/> / Explain _____	:	NO / <input type="checkbox"/> / 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 / X /

If yes, explain: _____

 jS/
Signature _____
Title: CSO

 7/9/98
Date

 jS/
Signature of Division Director

 8/3/98
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac
 HFD-150/DCATTERSON

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-671

Supplement # 004 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: HYCAMTINTM Action: AP AE NA
(TOPOTECAN) FOR INJECTION

Applicant SMITHKLINE Therapeutic Class 1
BEECHAM

Indication(s) previously approved OVARIAN CANCER - SECOND LINE

Pediatric information in labeling of approved indication(s) is adequate inadequate

Proposed indication in this application SMALL CELL LUNG CANCER - SECOND LINE

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing,
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. **(SEE ATTACHED COMMENTS FROM THE REVIEWING MEDICAL OFFICER.)**
5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from STEVEN HIRSCHFELD, MD, PHD (e.g., medical review, medical officer team leader)

Signature of Preparer and Title CSO

Date 8/6/98

Orig NDA/BLA # 20-671

HFD-150/Div File
NDA/BLA Action Package

HFD-006/ KRoberts

HFD-150/ CATTERSON

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

Edit Pediatric Information for this Submission

User Information

Preparer	STEVEN HIRSCHFELD
Title	REVIEWER
Division	HFD-150

Application Information

Application Number	20671	
Application Clock Date	1995-12-22 00:00:00	
Application Type	N	
Applicant Sponsor	SMITHKLINE	
Drug Trade Name	HYCANTIN	
Drug Generic Name	TOPOTECAN	
(leave supplement number, date and type blank, if original application)		
Supplement Number	1	
Supplement Date	1997-12-05	
Supplement Type	SE1 new INDICATION or significant modification e.g. switch to OT	
Regulatory Action	AP Approved	
Proposed Indication	small cell lung cancer. second line	
Adequacy of Proposed label for Pediatric Dosing	Does Not Apply	
Comments (please date)	Small cell lung cancer is extremely rare in children There is available therapy. .It is improbable that a study could be performed.	
Is there Pediatric Content?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<input type="button" value="Save && Continue"/> <input type="button" value="Clear"/>		

NDA 20-671
Hycamtin® (topotecan HCl)
Small Cell Lung Cancer Efficacy Supplement

Item 16: DEBARMENT STATEMENT

SMITHKLINE BEECHAM PHARMACEUTICALS HEREBY CERTIFIES THAT SAID APPLICANT DID NOT USE IN ANY CAPACITY THE SERVICES OF ANY PERSON DEBARRED UNDER SUBSECTION (A) OR (B) [SECTION 306(A) OR (B) OF THE ACT], IN CONNECTION WITH THE NEW DRUG APPLICATION FOR HYCAMTIN™ (TOPOTECAN HYDROCHLORIDE) FOR INJECTION. THE APPLICANT FURTHER CERTIFIES THAT NO SUCH PERSON DEBARRED BY THE FOOD AND DRUG ADMINISTRATION WILL BE USED IN ANY CAPACITY IN FUTURE INVESTIGATIONS INVOLVING THIS DRUG PRODUCT, AT SUCH TIME AS SAID DEBARMENT BECOMES KNOWN TO THE SPONSOR.