CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020305/S004

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-305/S-004

Name of Drug: Kytril (granisetron Hcl) Tablets

Sponsor: SmithKline Beecham Pharmaceuticals

Material Reviewed

Submission Date(s): July 27, 1998 [draft package insert (PI)]
September 25, 1998 (PI diskette)
January 27, 1999 (cartons)

Receipt Date(s): July 27, 1998
September 29, 1998
January 27, 1999

Background and Summary Description:

Kytril Tablets are currently approved as a 1 mg BID or, alternatively, a 2 mg once daily dose for the prevention of nausea and vomiting associated with emetogenic chemotherapy. It is currently approved in both a 1 mg and a 2 mg tablet, although the 2 mg tablet will not be commercially marketed [see June 8, 1998 Memorandum to the file (Supplement -003].

Supplement -004 was submitted to add prevention of nausea and vomiting associated with radiation as an approved indication. The proposed dose is 2 mg once daily. Both the March 29, 1999 medical and the June 7, 1999 statistical reviews recommend approval of the application.

Review

NOTE: THERE ARE SEPARATE PACKAGE INSERTS AND CARTONS FOR THE COMMERCIAL AND THE MILITARY (NON-MILITARY) PRODUCTS. THE 2 MG TABLET APPROVED IN S-003 IS TO BE PROVIDED TO THE MILITARY, AND WILL NOT BE AVAILABLE COMMERCIALLY. THE PACKAGE INSERTS DIFFER IN THAT THE DESCRIPTION AND HOW SUPPLIED SECTIONS OF THE COMMERCIAL PRODUCT TO NOT MENTION THE 2 MG TABLET AND THOSE SECTIONS OF THE PI TO BE SUPPLIED TO THE MILITARY DO NOT MENTION THE 1 MG TABLET. IN ADDITION, THE DOSAGE AND ADMINISTRATION SECTION OF THE MILITARY PI DOES NOT MENTION THE 1 MG DOSE OPTION.

PACKAGE INSERT-COMMERCIAL

The submitted package insert (PI) was compared to the currently approved labeling (KY:L3T, DATE OF ISSUANCE OCT 1997, approved with S-001). Other than those revisions proposed which are necessitated by the addition of a new indication, the following revisions have also been made:

1. Under the Hepatically Impaired Patients subsection of the Pharmacokinetic subsection of the PI, the last sentence has been revised to delete the bolded wording:

2. The HOW SUPPLIED section has been revised as follows:

   a. To delete the following bolded text in the first paragraph:

      Since this information is repeated directly below the non-bolded text, it is not necessary to have it repeated here. This is an acceptable revision.

   b. The NDC number for the 1 mg Unit-of-Use (2 tablets) package has been revised from

      This is an acceptable editorial revision.

In a meeting with the Dr. Hugo Gallo-Torres, GI Medical Team Leader, the firm's proposed labeling revisions necessitated by the new indication were discussed.

We faxed the firm our proposed revisions to the CLINICAL TRIALS section of the PI, and they responded with a counter proposal. See Attachment 1.

Their proposed revisions to the Total Body Irradiation subsection were acceptable with the exception of the proposed change from 22% (of patients who did not have vomiting over the entire 4 day period) to 28%. In a subsequent discussion, Dr. Olivia Pinkett, Regulatory Affairs, agreed that our percentage was appropriate if protection against emesis for the ENTIRE 4 day period was being described. See Attachment 2. According to Dr. Pinkett, in consultation with a statistician at SmithKline Beecham, the p value is not affected by this revision from 28% to 22%.

Their proposed revision to the Fractionated Abdominal Radiation subsection to reorder the paragraphs is not acceptable because the description of the secondary efficacy endpoint (which is more favorable to Kytril) should not be presented before the results of the primary efficacy endpoint (which states that Kytril was not found superior to placebo in patients receiving 20 cycles of radiation). The order of the paragraphs should remain as proposed by the firm in the initial July 27, 1998 submission. In addition, their proposal to have the statement, "The proportions of patients without emesis and without nausea for Kytril Tablets, compared to placebo were statistically..." is not acceptable since it states that the same patients had neither emesis or nausea. Although the p values for those patients who did not experience nausea and the patients who did not have nausea are the same, they are different populations.

PACKAGE INSERT-MILITARY

The package insert for the military is identical to the commercial except for the changes noted above. However, in the interim between now and the approval of S-003, the Department of Defense has revised their requirements for how the tablets can be packaged. Therefore, the cartons for the military will not be the same as those available commercially; the tablets will be available in 10 X 5 count blister strips (50 tablets per carton). See labeling review dated July 23, 1999 for S-003. As a result, the FPL submitted for S-004 will have to contain the revised cartons that will be available.

CARTONS-COMMERCIAL

The cartons for the 1 mg tablet were compared to those approved with supplement -001 on October 6, 1997. The following revisions have been made to both the 20 tablet Single Use Package and the 2 tablet Unit-of-Use Package:

1. The DOSAGE has been revised to add [redacted] This is an appropriate revision given that the indication is the subject of this supplemental application.

2. The sentence, [redacted] This revision complies with FDAMA and is therefore acceptable.

CARTONS-MILITARY

These were submitted prior to the finalization of the specifications by the Department of Defense. See the July 22, 1999 review of the labeling for S-003. The FPL labeling that will be submitted after approval of S-004 should be identical to that submitted for S-003 on March 30, 1999

BLISTERPACK FOIL-COMMERCIAL

These remain unchanged from the initial approval on March 16, 1995.

BLISTERPACK FOIL-MILITARY
These were submitted prior to the finalization of the specifications by the Department of Defense. See the July 22, 1999 review of the labeling for S-003. The FPL labeling that will be submitted after approval of S-004 should be identical to that submitted for S-003 on March 30, 1999.

Conclusions

The application can be approved on draft labeling. The firm should be requested to submit FPL identical in content to that submitted on the following dates, for the following components:

1. Package insert (commercial), submitted July 27, 1998, revised to contain the following CLINICAL TRIALS SECTION:

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The military (non-commercial) package insert should be identical to the commercial, revised to delete any reference to the 1 mg tablet and the associated dosage regimen, with the exception that the HOW SUPPLIED section should accurately reflect the available product(s).

2. Cartons and blister foil submitted January 27, 1999.

/S/ 7/23/99
Consumer Safety Officer

/S/ 7-26-99

ATTACHMENTS

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cc:
Original
HFD-180/Div. Files
HFD-180/KJohnson

draft: kj/July 17, 1999/c:\wpfiles\cso\n\20305s04.rkj

CSO REVIEW

31 pages
REDACTED
DRAFT
LABELING

C. Foreign Marketing History

Country	Indication for RINV	Comments
Austria	Prevention and treatment of chemotherapy and **radiotherapy** induced emesis and nausea.	
Italy	Prevention and treatment of acute and delayed nausea and vomiting induced by **cytostatic** therapy	Cytostatic represents chemotherapy and extrapolation to RINV
Netherlands	Prevention or treatment of acute nausea and vomiting associated with **cytostatic** therapy when administered on the day of treatment	Cytostatic represents chemotherapy and extrapolation to RINV
UK	Prevention and treatment of nausea and vomiting induced by **cytostatic** therapy	Cytostatic represents chemotherapy and extrapolation to RINV

EXCLUSIVITY SUMMARY FOR NDA # 20-103 SUPPL #_004

Trade Name _Kytril Tablets____ Generic Name __granisetron_____

Applicant Name _SmithKline Beecham_____ HFD # ___180_____

Approval Date If Known ____7/27/99_____

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 /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ 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 /_X__/ 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 /_X__/

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?

_____NO_____

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 /_X__/

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 /_X__/

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 /_X__/ NO /___/

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

NDA# ____20-103_____ _____

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 /_X_/ 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 /_X_/ 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 /__X_/

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(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:

Study 259

Study 448

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

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"):

_Study 259_____ _____

_Study 448_____ _____

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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 # [redacted] YES /__X_/ ! NO /___/ Explain: _____

_____

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Investigation #2

IND # [redacted] YES /__X_/ ! 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 /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ 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: _____

_____

/S/ 8/19/99

Signature Date

Title:

Supervisory, Project Management Staff, HFD-180

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/S/ 8-19-99

Signature of Office/ Date
Division Director

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

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DEBARMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, SmithKline Beecham hereby certifies that, to the best of its knowledge and belief, we did not use and will not use in any capacity, in connection with this supplemental application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-305/S-004

SmithKline Beecham Pharmaceuticals
Attention: Olivia Pinkett, PhD
1250 S. Collegeville Rd., P.O. Box 5089
Collegeville, PA 19426-0989

AUG - 5 1998

Dear Dr. Pinkett:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Kytril (granisetron HCl) Tablets

NDA Number: 20-305

Supplement Number: S-004

Therapeutic Classification: Standard (S)

Date of Supplement: July 27, 1998

Date of Receipt: July 27, 1998

This supplement proposes to add a 2 mg once daily dose for the prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 26, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 27, 1999.

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 443-0487.

Sincerely,

/S/ 8/5/98

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-305/S-004
HFD-180/Div. Files
HFD-180/K.Johnson
HFD-180/Holzbach
DISTRICT OFFICE

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Drafted by: KJ/August 5, 1998
filename: 20305S04.OKJ

SUPPLEMENT ACKNOWLEDGEMENT (AC)

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