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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-238

Medical Review(s)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	21-238
Sponsor:	GlaxoSmithKline Collegeville,PA.
Date Submitted:	August 30, 2000
Drug:	Kytril® (granisetron HCL)
Pharmacologic Category:	5-HT_3 Antagonist, antiemetic
Proposed Indication:	For the prevention of nausea and vomiting associated with chemotherapy and radiation
Material Submitted/Reviewed:	Vol. 4 and 7-11 a Bioequivalence Study, a Pediatric Study and references
Reviewer:	Raymond E. Joseph M.D., F.A.C.P., F.A.C.G.

BRIEF INTRODUCTION/BACKGROUND:

Kytril® (granisetron HCL), a 5-HT_3 receptor antagonist, is an antinauseant and antiemetic agent.

It is indicated for the prevention of:

1. Nausea and vomiting associated with the initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.

2. Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

The sponsor presented data to demonstrate that Kytril® (granisetron HCL) Oral Solution can be safely administered as an alternate dosage form to Kytril® Tablets to prevent nausea and vomiting in cancer patients receiving emetogenic chemotherapy. To support this claim the sponsor administered both dosage forms to normal volunteers in a bioequivalence study (Study 308).

Study 308

Forty healthy subjects (23 male and 17 female) were randomized to treatment, in a crossover fashion of replicate design, and received a total of 4 doses of Kytril®, 2 of tablet and 2 of Oral Solution.

All subjects were Caucasian with a mean age of 36 years (range 21 to 60). Two female subjects were subsequently withdrawn.

The adverse events of the normal volunteers in Study 308 are compared with adverse events of patients who used granisetron tablets for prevention of chemotherapy-induced nausea and vomiting.

The NDA population consisted of 1,450 cancer patients (Studies 215, 341, 402 and 436) undergoing chemotherapy who received 2 mg Kytril® Tablets (2 x 1mg). In the NDA studies, the majority of the patients were Caucasian (578 male and 872 female) with an age range from 18 to 88 years.

The most frequently reported adverse events (>5%) were:

Headache
Constipation
Fatigue

Findings:

- There were **no** significant differences between the tablet and the oral solution regimens in the number of adverse events.

- There were **no** deaths or serious adverse events in either treatment regimen.
- There were **no** withdrawals due to adverse events.

[Note]: The sponsor's pharmacokinetic conclusions were that with regard to AUC and Cmax, the oral liquid could be considered bioequivalent to the oral tablet. In addition, similar Cmax and median Tmax values show similarity of absorption of granisetron from the two formulations. (A full Biopharmaceutical review was pending at the time of this review.)

Study 028

Two hundred and ninety-four pediatric patients (177 males and 117 females), undergoing chemotherapy, were randomized to receive Kytril® Oral Solution, 20 mcg/kg or 40 mcg/kg, 60 minutes before chemotherapy with a second dose administered (6 to 12) hours later.

According to the sponsor, the adverse events experienced by the pediatric cancer patients were not compared to the adverse events of the adult NDA population because of the inherent differences of the target populations.

Of the 294 patients enrolled, 81 received 40 mcg/kg and 98 received 80 mcg/kg. The range of exposure was 20 mcg/kg to 400 mcg/kg.

The demographic characteristics at baseline were similar in the two treatment regimens.

Findings:

- There were **no** deaths during the course of treatment
- There were no clinically significant differences between the treatment regimens with regard to adverse events.
- There was no dose response with regards to serious Aes:
  - 10 patients in the 20 mcg/kg regimen reported a serious adverse event (7.0%) and 11 patients in the 40 mcg/kg reported a serious adverse event (7.3%) for a combined total of 38 serious adverse events.

- 3 patients in each treatment regimen withdrew due to adverse events (See table below).

Patients Withdrawn Due to Adverse Events - Study 028

Patient number	Age/ Gender	Adverse Experience	Intensity	Relationship
Kytril® 20mcg/kg group				
028.031.0463	9 F	agitation dyspnea myalgia	severe severe severe	prob unrelated prob unrelated prob unrelated
028.035.0319	1 F	vomiting	severe	prob unrelated
028.042.0013	15 M	thrombopenia intracranial hypertension	moderate severe	not related not related
Patient number	**Age/ Gender**	**Adverse Experience**	**Intensity**	**Relationship**
Kytril® 40mcg/kg group				
028.029.0223	3 F	rash	mild	possibly related
028.033.0098	11 M	hematemesis	moderate	prob unrelated
028.036.0327	14 M	vomiting	severe	possibly related

Reviewer Comments

- The adverse events profile for the Oral Solution is quite similar to the tablet formulation used in adults. Additionally, none of the 6 adverse events leading to withdrawal in the 20 mcg/kg regimen were thought to be related to the test medication, and of the 3 adverse events in the 40 mcg/kg regimen two were possibly related (rash and vomiting).

- The adverse event profile of the Oral Solution is comparable to the Tablet formulation as demonstrated in Study 308.

- The oral formulation appears to be reasonably safe in the pediatric Study 028. The adverse events seen in the children studied were similar to those reported in adult populations.

[Note]: No financial disclosure data were reviewed.

Recommendations for Regulatory Action

Pending any changes from the Agency's Biopharmaceutics department's bioequivalence review, the Kytril® Oral Solution represents an alternative dosage form to the Kytril® Tablets. Approval of the Kytril™ Oral Solution is recommended.

/S/ 5/2/01

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