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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-372

Pharmacology Review(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 23, 2003

FROM: Supervisory Pharmacologist
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 21,372 (Palonosetron)—Oral Carcinogenicity and Reproductive Toxicity Studies—Acceptability of Studies in Support of NDA for I.V. Injection

TO: NDA 21,372

The intended route of administration for palonosetron in humans is by intravenous injection. Generally, in toxicology studies, the drug is expected to be administered by the same route subject to practical considerations. In preclinical program, palonosetron was administered by oral gavage in mouse and rat carcinogenicity studies and reproductive toxicity studies in rats (Segment I. Fertility and reproductive performance, Segment II. Teratology and Segment III. Prenatal and postnatal) and rabbits (Segment II. Teratology). These studies are acceptable for the following reasons. Palonosetron has been developed under two INDS, one for i.v. (IND [redacted] (IND [redacted]) Dose selections for the carcinogenicity studies in mice and rats were based on maximum tolerated doses determined in 3-month oral toxicology studies. The Division and the CDER Executive CAC accepted them in 1994 and 1995. In the completed mouse carcinogenicity study, the systemic exposure to paolonosetron (plasma AUC) at the highest dose was about 150 to 289 times the human exposure (AUC =29.8 ng.hr/ml) at the recommended i.v. dose of 0.25 mg. In the rat carcinogenicity study, the systemic exposure at the high doses was 137 to 308 times the human exposure. Thus in both studies, the animals were exposed to sufficiently high doses. It is also impractical to administer the drug by i.v. injection daily for two years. The agency always accepted alternate routes of administration in the carcinogenicity studies as long as the dose selections are reasonably high.

In the reproductive toxicity studies, doses above 60 mg/kg/day were too toxic and lethal. Sufficiently high doses were employed in these studies assuring high systemic exposures as judged by the available toxicokinetic information from the other studies.

In conclusion, the oral carcingenicity and reproductive toxicity studies of palonosetron are acceptable in support of the NDA for palonosetron injection.

/S/

Jasti B. Choudary, B.V. Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

Cc:
NDA
HFD-180
HFD-181/CSO
HFD-150/Dr. Leighton
HFD-180/Dr. Choudary
HFD-180/Dr. Justice
HFD-180/Dr. Korvick

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/s/

Jasti Choudary
7/23/03 12:28:25 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 10, 2003

From: Yash M. Chopra
Pharmacologist, HFD-180

Subject: Safety limits for the impurities of [redacted] in Palonosetron

To: NDA 21-372

1. Two potential impurities in the final drug substance of palonosetron were identified by sponsor as [redacted] Sponsor has asked to set the upper limit of these impurities as [redacted] % in the final drug substance.

2. The intended clinical dose of palonosetron injection is 5 ug/kg for nausea and vomiting induced by cancer chemotherapy. As per the sponsor request, the amount of each of the impurities administered in the suggested single clinical IV dose will be [redacted]

3. The Division had suggested to sponsor to limit the amount of each of the impurities to [redacted] % and not [redacted] %. Sponsor did not conduct any preclinical toxicity studies with the purified impurities under NDA 21-372 and has now asked to set a limit of these impurities.

4. The safety limits for these impurities is estimated by computing the amounts of these impurities present in the 'no effect doses' of the available intravenous toxicity studies in a rodent and non-rodent. The 26-week IV toxicity study in rats (PALO-99-08) and 40-week IV toxicity study in dogs (PALO-99-10) were considered.

5. The 'no effect doses' in 26-week IV toxicity study in rats and 40-week IV toxicity study in dogs were 7 and 3 mg/kg/day, respectively. The batch # P30893-P105 of palonosetron was used in 26-week IV rat and 40-week IV dog toxicity studies and, a sample from this batch of the compound was reported to contain [redacted] and [redacted] % of [redacted] respectively (according to the certificate of analysis attached with the study). The study #, doses used and % impurities, no effect dose and amounts of impurities computed from the data of the certificate of analysis are shown below in the table:

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