

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020936

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
A 14-day oral toxicity study in female dogs

NDA: 20-936
Drug: Paxil CR (paroxetine hydrochloride)
Submission: 12-19-1997
Review Date: 2-4-1998
Reviewer Name: Nuoyu Huang
Division Name: Neuropharmacological drug products, HFD-120
Sponsor: SmithKline Beecham Pharmaceuticals
Drug Class: SSRI
Indication: Depression

TOXICOLOGY

A 14-DAY Oral Toxicity Study in Female Dogs (GI irritation test, protocol no. G95752, SB document no. BRL-029060/RSD-100531/1, GLP, QA)

Design

Drug: BRL 29060A enteric coated (batch number R5KO8F) and non enteric coated (batch no.R5KO8E), 20 mg tablets
Animal: 6-8 month old female beagle dogs, 9.3-15.3 kg, 6 dogs/group
Groups: 1) Control,
2) 20 mg/day enteric coated (1 tablet/day)
3) 20 mg/day non enteric coated (1 tablet/day)
4) 100 mg/day enteric coated (5 tablet/day)
5) 100 mg/day non enteric coated (5 tablet/day)
Treatment: oral tablet, 14 days, animals were killed and necropsied after overnight fast.

Results

Clinical Observations

Abdominal tenderness were found in 3/6 dogs in non-enteric coated HD group on day 3. Moderately subdued behavior was seen in 2/3 dogs in both HD groups (enteric- and non enteric- coated) on days 2 and 3.

Body Weight

No drug effect was observed.

Food Consumption

Food consumption was reduced consistently in non-enteric coated HD group beginning on day 2 of drug treatment.

Macroscopic Observations

No treatment-related finding was observed in the gastrointestinal tract.

Microscopic Observations

The following tissues were stained with hematoxylin and eosin and examined microscopically.

Tissues: caecum, colon, duodenum, ileum, jejunum, oesophagus, rectum, stomach

No treatment-related finding was observed.

Summary and Evaluation

The gastrointestinal irritative effect of enteric and non-enteric coated BRL 29060A was tested in female beagle dogs by oral tablet administration at doses of 20 and 100 mg/day for 2 weeks. Normal human dose of paroxetine is 20 mg/day. The study was adequately designed. No irritative or toxic effect was observed in the gastrointestinal track at the tested doses and formulations.

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ON ORIGINAL

Nuo-Yu Huang, Ph.D

cc. NDA 20936
HFD-120
/G.Fitzgerald
/N.-Y. Huang
/P. David

*/S/ 10/7/98 T.L. recommendation:
This study supports approval
of the NDA for a new dosage
form of Paxil*

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