CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-208

PHARMACOLOGY REVIEW(S)

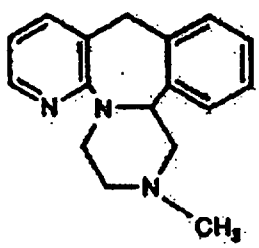
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom
Division Name: Neuropharmacological Drug Products
HFD# 120
Review Completion Date: September 19, 2000.

NDA number: **NDA 21-208**
Serial number/date/type of submission: N-000/Dec 30, 1999/Original application [new dosage form].
Information to Sponsor: Yes () No (X)
Sponsor (or agent): Organon Inc., 375 Mt. Pleasant Ave, West Orange, NJ 07052.
Manufacturer for drug substance: same.

Drug:

Code Name: ORG 3770.
Generic Name: mirtazapine.
Trade Name: Remeron® (mirtazapine) Orally Disintegrating Tablets.
Chemical Name: 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyridol[2,3-c] benzazepine.
CAS Registry Number: 61337-67-5.
Molecular Formula/ Molecular Weight: $C_{17}H_{19}N_3$ / 265.36 g/mol.
Structure:



Relevant INDs/NDAs/DMFs: ——— and NDA 20-415 for conventional oral tablets.

Drug Class: **CNS-active α1 adrenergic antagonist**, with potent antagonist activity at 5-HT_2 and 5-HT_3 serotonin receptors and H_1 histamine receptors and moderate antagonist activity at muscarinic acetylcholine receptors.

Indication: Depression.

Clinical formulation: Orally disintegrating tablets.

Route of administration: Oral (tablet disintegrates in mouth without water, but encapsulated drug dissolves in acid pH of stomach).

Proposed clinical protocol or Use: For the treatment of depression.

Previous clinical experience: Mirtazepine (Remeron® Tablets, 15, 30 and 45 mg) has been approved for treatment of depression.

Introduction and drug history: Mirtazepine has been approved as 15, 30 and 45 mg Remeron® Tablets for treatment of depression under NDA 20-415. The current submission is for a new formulation of "orally disintegrating tablets" that disintegrate in the mouth without water, but the encapsulated drug does not dissolve until reaching the acid pH of stomach. This application relies upon data previously submitted in support of NDA 20-415, plus demonstration of bioequivalence of the two formulations.

Studies reviewed within this submission:

- A 14-day gastrointestinal toxicity study with ——— tablets in dogs.

Studies not reviewed within this submission: none.

APPEARS THIS WAY
ON ORIGINAL

TOXICOLOGY:

General Comments: Toxicology studies supporting this NDA were reviewed for NDA 20-415. Although not requested by the Agency, the Sponsor has submitted a 14-day study in dogs to evaluate the gastrointestinal irritation potential of the orally disintegrating tablets. That study is reviewed below.

Study Title: **A 14-DAY GASTROINTESTINAL TOXICITY STUDY WITH [redacted] TABLETS IN DOGS.**
Study No: 1753/XT023.
Amendment #, Vol #, and page #: N-000, vol 1.10, pp 6-65.
Conducting laboratory and location: [redacted]

Date of study initiation: Jun–Jul 1999 [in life part of study].
GLP compliance: yes.
QA- Report: Yes (X) No ()

METHODS:

Dosing:

- species/strain: Pure-bred, adult, HSD/HFR:DOBE, beagle dogs [redacted]
- #/sex/group or time point: 3 dogs/sex received drug; 2/sex were left untreated to serve as controls.
- age: 8-9 mo old.
- weight: males 10.5 kg, females 9.2 kg, at start of dosing.
- satellite groups used for toxicokinetics or recovery: none.
- dosage groups in administered units: 150 mg Remeron (as 5 [redacted] tablets) per day; controls were untreated.
- route, form, volume, and infusion rate: 5 30 mg orally disintegrating tablets (denoted ' [redacted] in this study). Administration to dogs was accomplished by putting the tablets on their tongues and holding their mouths closed for 30 sec to 2 min (occasionally a small amount of water was introduced into the mouth when disintegration was not obtained in this time frame).
- housing: Dogs were housed individually and given water *ad libitum* and 300 g of food per day; food was withheld 16 hours prior to terminal sacrifice. The report did not specify the time of day of feeding or dosing.

Drug, lot#, radiolabel, and % purity: batch CP 099106 (lot number 990017; IPA 99021), manufactured at Cima Labs Inc, Eden Prairie, MN. The [redacted] tablets used in this study were the same batch/lot used in the clinical bioequivalency Study 22527, comparing this formulation to the conventional Remeron tablets that have already been approved (NDA 20-415).

Formulation/vehicle: orally disintegrating tablet; disintegrates rapidly in the mouth, with "a nice orange taste." According to the Sponsor "...the bitter taste of the active

ingredient is masked by coating the active ingredient particles with [redacted] an acrylic polymeer that is impermeable at pH 7 in the mouth and rapidly swells at pH 1-5, enabling a fast dissolution in the stomach. The fast disintegration of the tablet in the mouth is achieved by an effervescent system present in the tablet formulation."

Observations and times: Clinical observations, body weights, food consumption, clinical pathology were measured at various times during the study. At the end of the study (~24 hr after the last dosing) all dogs were killed, autopsied and examined for abnormalities; histopathological examination was limited to sites of treatment (tongue and both sides of the buccal cavity) and gastro-intestinal tract from esophagus to rectum.

- Clinical signs: daily at various time (before dosing and usually up to 6 h after dosing) throughout the study for any behavioral and physical abnormalities. Physical exams were performed during predosing period and at the end of the dosing period.
- Body weights: weekly, prior to daily feeding procedure.
- Food consumption: determined daily by subtracting the amount of food left from the amount of food supplied; monitored qualitatively daily at ~1 and 24 h after feeding; reported as mean daily food consumption once a week throughout the study.
- Ophthalmoscopy: not performed.
- EKG: not performed.
- Hematology: not performed.
- Clinical chemistry: not performed.
- Urinalysis: not performed.
- Organ weights: not performed.
- Gross pathology: at necropsy at the end of the dosing period (presumably ~24 h after 14th dose), following exsanguination at the right and left axillary vessels under deep pentobarbital anesthesia. For organs autopsied see table in Addendum 1.
- Organs weighed: not performed.
- Histopathology: For organs examined for histopathology, see table in Addendum 1.
- Toxicokinetics: not performed.

RESULTS:

- *Mortalities:* There were no unscheduled deaths.

- *Clinical observations (daily, before dosing and up to 6 hrs after dosing; standard physical exams before starting dosing and at end of dosing period, 1-5 hr after dosing)*

Treatment-related effects were limited to slight hypoactivity in 1/3 males after first dosing, slight tremors in 1/3 females during first 2 days of dosing, rare to occasional bouts of diarrhea in 2/3 males and 2/3 females, and rare yellow vomiting in 1/3 females. [One control female and one dosed female were treated for purulent conjunctivitis, with topical rifamycin, during the first week.] One dosed female (F2004) showed symptoms of being in heat at the end of the dosing period (see gross pathology below); the Sponsor does not consider this drug-related.

- *Body weights (weekly, prior to feeding; 2 weeks before dosing and throughout dosing period)*

There were no treatment-related alterations in body weights; all dogs gained weight over the 2 weeks of the study (1-7%).

- *Food consumption (daily, but reported as average daily value per week; 2 weeks before dosing and throughout dosing period)*

There were no treatment-related alterations in food consumption. All males ate all available food throughout the study; some females failed to consume all available food, but this was not treatment-related.

- *Gross pathology (all dogs were autopsied and examined for abnormalities)*

There were no apparent treatment-related alterations; lung pathology in 1/3 dosed females (red area on surface of left diaphramatic lobe), 1/3 dosed males (a few gray foci on surface of left intermediate lobe), and 1/2 control females (white area on surface of left apical lobe); evidence that 2/3 dosed females (F2004 and F2006)) were in heat (corpora lutea, thickened uterine wall, thickened vaginal mucosa, and slight mammary gland development, with red areas around nipples).

- *Histopathology (all dogs: tongue at 5 levels from tip to base; left and right buccal mucosa at 5 levels throughout the tissue; esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum at 3 levels)*

The number of dogs tested is small, but no major treatment-related alterations were apparent. Findings in dosed dogs were limited to minimal granulocyte infiltrations of tongue and buccal mucosa that may or may not be present at slightly higher frequencies

or extents than in controls (the Sponsor says not). [Checked/verified with Jennifer Burris, D.V.M., 2/8/2000]

Comparison of dose of Remeron administered to dogs in this study (150 mg/d) to the maximum recommended dose in humans (45 mg/d).

SPECIES	DOSE/DAY		
	mg	mg/kg	mg/m^2
Dog (10 kg)	150 (/10→)	15 (x20→)	300
Human (60 kg)	45 (/60→)	0.75 (x37→)	28
Ratio, Dog:Human	3.3X	20X	11X

KEY STUDY FINDINGS:

Although the number of dogs tested in this study is small (6 drug-treated and 4 controls), the results suggest that the orally disintegrating formulation of Remeron does not produce local toxicity at the sites of treatment (tongue and mouth) or in the rest of the gastro-intestinal tract when administered to dogs daily for 2 weeks at a dose of 150 mg per day; that is 11 times the maximum recommended daily human dose on a mg/m^2 basis.

ADDENDUM LIST:

- Addendum 1: Histopathology Inventory for NDA 21-208.

Addendum 1

Histopathology Inventory for NDA 21-208 *

Study: 14-d Species:Beagle dogs	Gross Anatomy	Histopathology
Adrenals	X	
Aorta	X	
Bone Marrow smear		
Bone (femur)	X	
Brain	X	
Buccal cavity	X	X (each side)
Cecum	X	X
Cervix		
Colon	X	X
Diaphragm	X	
Duodenum	X	X
Epididymis	X	
Esophagus	X	X
Eye	X	
Fallopian tube	X	
Gall bladder	X	
Gross lesions		
Harderian gland		
Heart	X	
Hyphophysis		
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	X	
Lachrymal gland		
Larynx		
Liver	X	
Lungs	X	
Lymph nodes, cervical	X	
Lymph nodes mandibular	X	
Lymph nodes, mesenteric	X	
Mammary Gland	X	
Nasal cavity		
Optic nerves	X	
Ovaries	X	
Pancreas	X	
Parathyroid	X	
Peripheral nerve	X	
Pharynx		
Pituitary	X	
Prostate	X	
Rectum	X	X
Salivary gland	X	
Sciatic nerve		
Seminal vesicles		
Skeletal muscle	X	
Skin	X	
Spinal cord	X	
Spleen	X	
Sternum	X	
Stomach	X	X
Testes	X	
Thymus	X	
Thyroid	X	
Tongue	X	X
Trachea	X	
Urinary bladder	X	
Uterus	X	
Vagina	X	
Zymbal gland		

* no organ weights reported.

SUMMARY/CONCLUSIONS:

This drug (mirtazapine) is already marketed as Remeron® in conventional tablets of 15, 30 and 45 mg for the treatment of depression (under NDA 20-415). The submission currently under review (NDA 21-208) is for a new formulation of orally disintegrating tablets that will contain the same amounts of drug as the marketed, conventional tablets. The Chemistry Reviewer (Dr. Sherita McLamore) has determined that there are no new impurities in the orally disintegrating tablet formulation requiring qualification (personal communication, September 18, 2000). The Biometrics Reviewer (Dr. Hong Zhao) has concluded that the orally disintegrating tablet formulation has been determined to be bioequivalent to the marketed, conventional tablets (personal communication, September 18, 2000). Consequently, the preclinical data that was reviewed for the original NDA (NDA 20-415) is considered adequate for approval of this new formulation.

The Sponsor's proposed labeling relating to preclinical data is identical to that already approved for NDA 20-415. This pertains specifically to "Pharmacodynamics" in the "Clinical Pharmacology" section; the entire "Carcinogenesis, Mutagenesis, Impairment of Fertility" section; "Pregnancy Category C" in the "Pregnancy" section.

RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, there are no objections to the approval of this NDA.

/S/ 9/20/00

Linda H. Fossom, Ph.D./Pharmacologist

Cc:
NDA orig (21-208)
Div file
HFD-120
/GFitzgerald 9/22/00
/LHFossom
/PDavid