CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-793

PHARMACOLOGY REVIEW

MEMORANDUM

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

DATE: May 31, 2005

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

SUBJECT: NDA 21,793 (Reglan/ Metoclopramide Orally Disintegrating Tablet) - Supervisory Pharmacologist's Addendum to May 20, 2005 Pharmacology Review of Dr. Y. M. Chopra- Recommended Final Labeling Changes- Corrections to Dr. Chopra's Review

TO: NDA 21,793

This Supervisory Addendum will address the final labeling changes for the preclinical portions of the labeling and corrections to Dr. Chopra's May 20, 2005 Pharmacology review. The incorrect portions are cited by page and line numbers of his review and correct information provided. These have been discussed with Dr. Chopra on May 23, 2005.

The sponsor in the present submission for metoclopramide orally disintegrating tablet (ODT) is relying on the Agency's finding of safety and efficacy for their previously approved Reglan 5 and 10 mg tablets under NDA 17,584. In as much as bioequivalence has been established between 10 mg metoclopramide ODT and the approved raglan 10 mg tablet, Pharmacology recommends that the present application be approved based on the finding of safety for 10 mg raglan tablet under NDA 17,854. The sponsor provided published reports of additional genotoxicity testing of metoclopramide and study of its tumor promoting potential in rats. The positive results from these studies and the previous finding of tumorigenicity should be considered as nonclinical safety issues relevant to clinical use, i.e. positive findings in the in vitro CHL/HGPRT forward mutation test and the in vitro human lymphocyte chromosome aberration test and the in vivo tumor promoting effect in rats.

LABELING:

PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 77-week study was conducted in rats with oral doses of metoclopramide up to 40 mg/kg/day (about 5 times the maximum recommended human dose on surface area basis). Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is

contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

In a rat model for assessing the tumor promotion potential, a two- week oral treatment with metoclopramide at a dose of 260 mg/kg/day (about 35 times the maximum recommended human dose on surface area basis) enhanced the tumorigenic effect of N-nitrosodiethylamine.

Metoclopramide was positive in the in vitro Chinese hamster lung cell /HGPRT forward mutation assay for mutagenic effects and the in vitro human lymphocyte chromosome aberration assay for clastogenic effects. It was negative in the in vitro Ames mutation assay, the in vitro unscheduled DNA synthesis (UDS) assay with rat and human hepatocytes and the in vivo rat micronucleus assay.

Metoclopramide at intramuscular doses up to 20 mg/kg/day in male and female rats (about 3 times the maximum recommended human dose on surface area basis) was found to have no effect on fertility and reproductive performance.

Pregnancy. Teratogenic Effects:Pregnancy Category B.

Teratology studies have been performed in rats at oral doses up to 45 mg/kg/day (about 6 times the maximum recommended human dose on surface area basis) and in rabbits at oral doses up to 45 mg/kg/day (about 12 times the maximum recommended human dose on surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother. Because of the potential for serious adverse reactions in nursing infants from metoclopramide and because of the potential for tumorigenicity and tumor promoting potential shown for metoclopramide in rats, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

CORRECTIONS to Dr. Chopra's Review of May 20, 2005:

Page 4, Lines 1 to 6

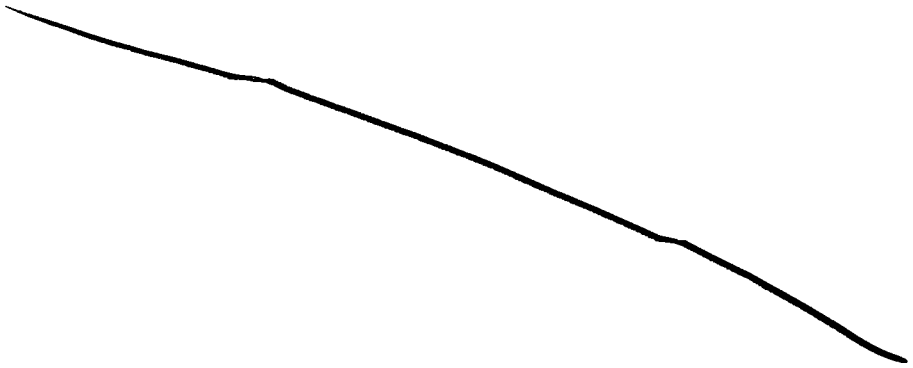
1 Page(s) Withheld

_____ Trade Secret / Confidential

✔ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox- 1



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

Cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Chopra
HFD-180/Dr. Korvick

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/s/

Jasti Choudary
5/31/05 11:51:44 AM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-793**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/2/04**
PRODUCT:	**Metoclopramide Orally Disintegrating 5 and 10 mg Tablets**
INTENDED CLINICAL POPULATION:	**Adults patients with gastroesophageal reflux or diabetic gastroparesis.**
SPONSOR:	**Schwarz Pharma, Inc., Mequon, WI.** (SPInc)
DOCUMENTS REVIEWED:	**Vol. 1.1 and 1.8**
REVIEW DIVISION:	**Division of Gastrointestinal and Coagulation Drugs Products (HFD-180)**
PHARMACOLOGY & TOXICOLOGY REVIEWER:	**Yash M. Chopra, M.D., Ph.D.**
PHARMACOLOGY & TOXICOLOGY SUPERVISOR:	**Jasti B. Choudary, B.V.Sc, Ph.D.**
ACTING DIVISION DIRECTOR:	**Joyce Korvick, M.D, M.P.H.**
PROJECT MANAGER:	**Susan Daugherty, B.S.N.**

DATE OF REVIEW SUBMISSION TO DIVISION FILE SYSTEM (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: From a preclinical standpoint, the approval of the application is recommended.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: The changes suggested in the labeling section of the review should made.

II. Summary of nonclinical findings

Brief overview of nonclinical Findings:

A. Pharmacology:

Metoclopramide a prokinetc agent, increases the tone and amplitude of contractions of gastrointestinal tract and enhanced rapid gastric emptying by blocking the central and peripheral D_2 receptors and 5-HT_3 receptors and, by a 5-HT_4 agonist effects. Its effects on the secretions of gastrointestinal tract were insignificant. The anti-emetic and anti-nauseant effects of the compound were due to the blocking chemoreceptor trigger zone (CTZ). It was seen to cause prolactin release in animal studies. Metoclopramide actions were not via vagal stimulation.

B. ADME: No new study was submitted. Orally administered metoclopramide was seen to be rapidly absorbed and attained its plasma peak in 1 to 2 hr, about 20 to 30% of the compound was bound to protein and its absolute bioavailability was 80% in rats. In man, a bioequivalence study with the proposed preparation, showed that the plasma concentrations ($AUC_{0\text{-}inf in}$ values) were similar to currently marketed metoclopramide tablet as the AUC values were 357$\pm$147 ng.hr/ml and 368$\pm$136 ng.hr/ml by the proposed 10 mg ODT and 10 mg currently marketed metoclopramide tablet, respectively.

C. TOXICOLOGY:

The 6-, 14- and 16- week toxicity studies in rats were conducted from the dose of 2 to 80 mg/kg/day. The animals treated with metoclopramide showed treatment related reduced general activity without any histopathological adverse effect. The central nervous system was the identified target organ of toxicity in these studies.

In dogs, two 16-week oral toxicity studies and 54-week oral toxicity study were conducted from the doses of 5 to 80 mg/kg/day. A dose related reduced activity, tremor and slight increase in liver weight of animals was noted. A slight tachyacardia without any EKG effect was seen. The toxicity of liver enlargement, rarefaction and increased glycogen suggested liver as the target organ of toxicity in dogs.

The reproductive segment. I (Fertility and general reproductive performance toxicity) study in rats, segment II (teratology in mouse, rats and rabbits) and segment III. Prenatal and postnatal studies in rats were conducted by intramuscular route of administration. Metoclopramide was administered up to 20 mg/kg/day in these studies. No adverse effects related to reproductive or fertility parameters or developmental toxicity were observed in animals.

Sponsor did not conduct 2-year carcinogenicity studies in rat or mouse, but in a 77-week rat oral chronic toxicity study, treatment related mammary adenocarcinoma tumor was seen in 1 male rat of high dose of 40 mg/kg/day (240 mg/mm^2/day).

The genotoxicity of the compound was assessed on Ames test, HGPRT assay using V79 Chinese hamster lung cells. It was not mutagenic in Ames test but an increased number of TG resistant mutant frequencies were noted in hypoxanthine guanine phosphoribosyl transferees (HGPRT) mutation assay using V79 cells. Metoclopramide was positive in HGPRT assay using human or rat hepatocytes and induction of micronuclie in human lymphocytes. Metoclopramide was clastogenic in hypoxanthine guanine phosporibosyl transferase (HGPRT) mutation assay and in the induction of micronuclei in human lymphocytes and it was a promotor of liver tumors in rats in a Solt-Farber assay

D. Nonclinical safety issues relevant to clinical use: None

PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

Metoclopramide hydrochloride (Reglan®) a prokinetic agent which acts on the upper gastrointestinal tract was shown to be an effective antinauseant and anti-emetic agent. NDA 17-854 (Wyeth-Ayerst) for Reglan 10 mg tablets was approved in 1980. A liquid product was also approved but was withdrawn and no longer available. The oral form has been indicated for the short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux disease (GERD) those did not respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. A supplement for NDA 17-854 for Reglan 5 mg tablets was approved on 5/05/1987 and subsequently; the NDA was transferred to SPInc on 12/27/2001. None of available metoclopramide preparation was suitable for adults who can not swallow tablet; therefore the sponsor submitted the present application on orally disintegrating tablet

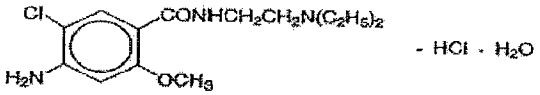
NDA number: 21-793
Review number: 1
Sequence number/date/type of submission: 000/7/30/04/
Information to sponsor: Yes (X)
Sponsor and/or agent: Schwarz Pharma Inc., Mequon, WI.
(SPInc)
Manufacturer for drug substance: Schwarz Pharma Inc., Mequon, WI.
Reviewer name: Yash M. Chopra, MD, Ph.D.
Division name: Gastrointestinal & Coagulation Drugs Products
HFD #: HFD-180
Review completion date: May 20, 2005

Drug:

Trade name: Reglan [redacted] Tablets
Generic name: Metoclopramide Orally Disintegrating Tablets

Code name: --
Chemical name: 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydochloride monohydrate
CAS registry number: 54143-57-6
Molecular formula/molecular weight: $C_{14}H_{22}ClN_3O_2.HCl.H_2O/354.3$

Structure:



Relevant INDs/NDAs/DMFs: NDA 17-854

Drug class: Prokinetic agent/D_2 receptor antagonist/5-HT_3 receptor antagonist/5-HT_4 receptor agonist

Intended clinical population: Adults with symptomatic gastroesophageal reflux who fail to respond to conventional therapy

Clinical formulation: Each of the orally disintegrating tablet contains 5 or 10 mg metoclopramide and diluents (mannitol EZ, USP and mannitol 60 USP) and other excipients like microcrystalline cellulose NF/EP, magnesium stearate NF/EP/JP, crospovidone K-30 USP/EP, aspartame NF/EP/JPE and natural and artificial flavoring agent SN027512 and silicon dioxide NF/EP. The amounts of excipients in the proposed 10 mg tablets formulations are two times the amounts present in 5 mg proposed tablets. The quantities in the formulations were within the generally recognized as safe (GRAS) limits, therefore safe. The rapidly disintegrating tablets are of high porosity and fragility.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-793 are owned by Schwarz Pharma, Mequon, WI. The sponsor acquired Reglan tablets (5 and 10 mg metoclopramide tablets) NDA 17-854 on December 27, 2001. All data and information discussed below and necessary for approval of NDA 21793 were now owned by SPIn.

Studies reviewed within this submission:

Sponsor made a reference to November 8, 2002 meeting with the Agency and stated that the preclinical studies submitted with the Reglan tablets (3 and 10 mg metoclopramide tablets - NDA 17-854) should be considered. The following additional information on metoclopramide was submitted with the present NDA:
1. A copy of the approved label of metoclopramide (Reglan) tablets,
2. The text description of metoclopramide in the textbook of Goodman & Gilman's The Pharmacological basis of therapeutics, 10^{th} Edition,

3. A research publication on the 'Testing of Metoclopramide and Procainamide for their ability to induce Genotoxic effects in cultured Mammalian Cells, Toxicol & Applied Pharmacol. 131: 185-191, 1995,
4. A research publication on the 'Evaluation of DNA-Damaging, Clastogenic and Promoting Activities of Metoclopramide and Procainamide in Rats'. Toxicol & Applied Pharmacol. 131: 192-197, 1995,

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Metoclopramide acts to stimulate contractions of the gastrointestinal motility by inhibiting dopaminergic mechanisms, by the antagonism of 5-HT_3 receptors and stimulation of excitatory neurons via 5-HT_4 receptors and thus manifest the unopposed central cholinergic activity. This leads to an increased release of acetylcholine from enteric neurons, suppress the interneurons. It also acts as anti-emetic by inhibiting dopamine induced stimulation of chemoreceptor trigger zone (CTZ). It was observed to have only insignificant or no effect on gastric, hepatic or pancreatic secretions.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Metoclopramide acts by increasing the gastrointestinal motility by inhibiting dopaminergic mechanisms and thus manifest the unopposed central cholinergic activity. This leads to an increased release of acetylcholine from enteric neurons, suppress the interneurons by the antagonism of 5-HT_3 receptors and stimulation of excitatory neurons via 5-HT_4 receptors. The prokinetic effect of the compound was due to the blocking of both central and peripheral dopaminergic receptors, by the 5-HT_3 receptors blocking and 5-HT_4 receptors stimulating effects. The anti-emetic and anti-nauseant effects of the compound were predominantly by blocking the central dopaminergic D2 receptors on cholinergic enteric neurons and chemoreceptor trigger zone (CTZ). Metoclopramide induced release of prolactin and may cause transient aldosterone release (fluid retention). Sponsor did not submit any new preclinical study with the present submission.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Metoclopramide was absorbed rapidly and attained a plasma peak within 1 to 2 hr and about 20 to 30% of the compound was bound to protein. The absolute bioavailability in comparison to intravenous route, was 80% in rats. In man, a bioequivalence study with the proposed preparation, showed that the plasma concentrations ($AUC_{0\text{-}infin}$ values) were similar to currently marketed metoclopramide tablet as the AUC values were 357±147 ng.hr/ml and 368±136 ng.hr/ml by the proposed 10 mg ODT and 10 mg currently marketed metoclopramide tablet, respectively. The rapidly administered compound when

taken without water (to allow dissolution) achieved plasma peak in similar time of 1.88 hr. Metoclopramide 10 mg dose (0.2 mg/kg) as tablet (reference compound) and 10 mg dose of the proposed rapidly disintegrating tablet given with or without water achieved a similar bioequivalence of the compound.

2.6.6 TOXICOLOGY

No new general toxicology studies were submitted with present submission and sponsor referred to acute, subacute, chronic toxicity studies submitted with NDA 17-854 (metoclopramide tablets). The pharmacology reviews of the NDA was available. In the present submission, a toxicological expert report and the revised summary of the preclinical toxicity studies were submitted.

2.6.6.4 Genetic toxicology

Two research publications on the genotoxicity studies of metoclopramide were submitted with the application. These are entitled as "Testing of Metoclopramide and Procainamide for their ability to induce Genotoxic effects in cultured Mammalian Cells" and, "Evaluation of DNA-Damaging, Clastogenic and Promoting Activities of Metoclopramide and Procainamide in Rats".

2.6.6.4.1 Study title: Testing of Metoclopramide and Procainamide for their ability to induce Genotoxic effects in cultured Mammalian Cells. Martelli, A., Campart, G.B. et al, Toxicol. & Applied Pharmacol. 131: 185-191, 1995.

Key findings: Metoclopramide was mutagenic in the HGPRT assay with V79 Chinese hamster lung cells and it was clastogenic in the micronucleus induction test in human lymphocytes.

The study included the evaluation of the genotoxicity of Metoclopramide on: (i) DNA fragmentation in primary cultures of SD rat hepatocytes,

ii. Human hepatocyte for DNA repair assay

iii. HGPRT assay in V79 Chinese hamster lung cells (for induced frequency of TG resistance - TG^r)

iv. Induction of micronuclei in Human lymphocytes

i. **The determination of DNA fragmentation in primary cultures of SD rat hepatocytes**:

Cell line/Cells Used: i. The determination of DNA fragmentation in primary cultures of SD rat hepatocytes,

Doses used in definitive study:
Metoclopramide was used at 0.10, 0.18 and 0.32 mM concentrations for rat hepatocytes and, 0.18 and 0.32 mM concentrations for human hepatocytes for the determination of

DNA fragmentation and repair. The DNA fragmentation evaluated by alkaline elution technique.

Basis of dose selection: Not provided

Negative controls: Direct Culture medium

Positive controls: N-nitrosodiummethylamine (NDMA) for tests # (i) and (ii).

Incubation with Metoclopramide and sampling times: (i) DNA fragmentation in primary cultures were exposed for 20-hr, (ii) Human lymphocytes for DNA repair synthesis primary culture assay- 20 hr exposure

Results

Study outcome: In cytotoxicity assay, 30% reduction in trypan blue-excluding rat hepatocytes was seen at 0.56mM metoclopramide. The highest concentration in mutagenicity assay used was 0.32 mM metoclopramide.

In DNA damage/in alkaline medium assay, the compound did not affect the DNA elution rates of rat or human hepatocytes preparation. The elution rates were 23.1, 24.5, 24.4 and 24.9% at 0, 0.10, 0.32 and 1.00 mM concentrations in rat hepatocytes and, 30.9, 31.3 and 32.6% at 0, 0.1 and 1.0 mM in human hepatocytes (85.2 and 82.5% in rat and human cultures assays) as shown below sponsor's table 1 (vol 1.8, pp 066).

TABLE 1

DNA Fragmentation in Primary Cultures of Rat and Human Hepatocytes Following 20 hr Exposure to MCA or PCA as Evaluated by the Alkaline Elution Technique

Treatment conditions (mM)	% DNA eluted from the filter (means ± SD)[a]	K_r/K_c[b] (means ± SD)[a]
	Rat hepatocytes	
Control	23.1 ± 1.95	(K_c = 0.202 ± 0.0020)
MCA		
0.10	24.5 ± 1.43	1.07 ± 0.09
0.18	24.4 ± 2.23	1.06 ± 0.07
0.32	24.9 ± 2.80	1.09 ± 0.09
PCA		
0.18	23.8 ± 1.74	1.04 ± 0.08
0.32	23.4 ± 2.06	1.02 ± 0.08
0.56	24.8 ± 3.20	1.09 ± 0.13
NDMA 5	85.2 ± 3.96[c]	7.39 ± 1.01
	Human hepatocytes (case 2)	
Control	30.9 ± 1.80	(K_c = 0.0284 ± 0.0021)
MCA		
0.18	31.3 ± 1.04	1.01 ± 0.04
0.32	32.6 ± 2.93	1.07 ± 0.12
PCA		
0.32	32.7 ± 2.36	1.07 ± 0.09
0.56	33.0 ± 3.31	1.17 ± 0.14
NDMA 5	82.5 ± 2.23	4.72 ± 0.36

[a] Values of rat hepatocytes are the means of determinations carried out in triplicate on cultures obtained from three rats. Values of human hepatocytes are the means of determinations performed on three cultures.

[b] K_r/K_c is the relative DNA elution rate calculated as described under Materials and Methods.

[c] Significance level was determined by the use of the nonparametric Wilcoxon two-sample two-tailed test (Rümke and De Jonge, 1964): $p < 0.002$.

Metclopramide did not induce DNA fragmentation in rat hepatocyte culture.

(ii) **DNA repair assay using human hepatocytes**:

Metoclopramide concentrations used: 0.10, 0.18 and 0.32 mM for rat and human hepatocytes preparations.

Basis of dose selection: Not provided

Negative controls: Direct Culture medium

Incubation with Metoclopramide and sampling times: Human lymphocytes for DNA repair synthesis primary culture assay- 20 hr exposure

Results:

The cytoplasmic and nuclear grain counts were not increased up to the concentration of 0.32 mM metoclopramide. But in 1 of the 3 human liver cultures, the grains were increased and the test was positive and the test was negative in the remaining 2 hepatocyte samples. The non-dose related positive results in the increase in net nuclear grains in one human hepatocyte culture were due to the changes occurred in the liver sample of the cholestasis patient (sample used in the assay). The results are shown in the table # 2 (sponsor submission vol 1.8, pp 067).

TABLE 2
DNA Repair Synthesis in Primary Cultures of Rat and Human Hepatocytes Following 20 hr Exposure to MCA or PCA as Evaluated by Autoradiography

Treatment conditions (mM)	NUC (means ± SD)	CYT (means ± SD)	NNG (means ± SD)	% Repair
Rat hepatocytes				
Control	15.0 ± 6.9	16.3 ± 7.2	−1.3 ± 4.9	11.7 ± 4.7
MCA				
0.10	15.8 ± 6.9	16.3 ± 7.1	−0.5 ± 4.8	14.2 ± 4.4
0.18	14.1 ± 5.3	14.4 ± 5.7	−0.3 ± 4.3	14.0 ± 4.3
0.32	11.9 ± 4.7	11.7 ± 4.8	0.2 ± 4.6	16.7 ± 3.7
PCA				
0.18	15.8 ± 5.5	16.4 ± 5.8	−0.6 ± 4.3	10.0 ± 4.8
0.32	11.8 ± 5.1	12.3 ± 5.3	−0.5 ± 4.3	12.5 ± 4.8
0.56	14.3 ± 5.5	14.4 ± 5.9	−0.1 ± 4.4	11.0 ± 7.0
NDMA 5	63.7 ± 20.9	20.0 ± 9.5	43.7 ± 14.6*	100
Human hepatocytes				
Case 1				
Control	11.2 ± 6.5	8.9 ± 4.1	2.3 ± 5.8	27
MCA				
0.10	13.0 ± 6.4	6.5 ± 3.0	6.5 ± 5.8*	63
0.18	10.1 ± 5.3	5.9 ± 3.6	4.6 ± 5.8**	49
0.32	9.5 ± 5.3	4.4 ± 2.9	5.1 ± 6.4**	45
PCA				
0.18	14.1 ± 7.1	5.7 ± 2.5	8.4 ± 6.6*	65
0.32	11.2 ± 5.7	5.2 ± 2.4	6.0 ± 5.5*	57
0.56	14.7 ± 6.6	5.3 ± 3.1	9.5 ± 6.5*	76
NDMA 5	71.3 ± 24.4	10.7 ± 6.5	60.6 ± 21.0*	100
Case 2				
Control	10.3 ± 5.6	11.5 ± 4.0	−1.0 ± 4.5	
MCA				
0.10	12.6 ± 4.4	14.0 ± 5.1	−1.4 ± 4.8	
0.18	11.1 ± 4.6	11.2 ± 4.8	−0.1 ± 4.3	13
0.32	11.9 ± 4.7	12.5 ± 5.3	−0.6 ± 4.5	12
PCA				
0.18	10.4 ± 4.3	10.2 ± 4.2	0.2 ± 4.3	18
0.32	11.4 ± 5.5	13.0 ± 5.9	−1.6 ± 4.3	7
0.56	13.0 ± 5.5	14.8 ± 5.8	−1.8 ± 4.9	12
NDMA 5	62.8 ± 23.7	17.1 ± 10.6	45.7 ± 19.1*	100
Case 3				
Control	9.3 ± 4.5	6.8 ± 3.4	2.5 ± 4.5	35
MCA				
0.18	10.4 ± 5.2	7.3 ± 3.8	3.1 ± 4.3	34
0.32	10.9 ± 5.2	7.7 ± 3.7	3.2 ± 4.3	41
PCA				
0.32	9.2 ± 4.3	6.9 ± 3.1	2.3 ± 3.9	31
0.56	9.5 ± 4.1	7.1 ± 3.9	2.4 ± 3.9	29
NDMA 5	48.8 ± 20.9	8.5 ± 5.4	33.3 ± 16.8*	100

Note: abbreviations used: NUC, nuclear grain count; CYT, cytoplasmic grain count; NNG, net nuclear grains. Grain counts include cells with no nuclear labeling encountered in the 50 cells counted for each slide. Counts of 100 cells from duplicate autoradiographs were carried out for each dose level. Rat values are the means of data obtained from three animals. The % repair is the percentage of cells with net nuclear labeling ≥5 grains. Statistical significance of the difference from corresponding control value was evaluated according to the method for comparison of means of two samples of large size described by Bailey (1959): *$p < 0.001$; **$p < 0.01$.

Metclopramide did not induce DNA fragmentation in human hepatocyte culture.

iii. **HGPRT assay in V79 Chinese hamster lung cells (for induced frequency of TG resistance - TG^r)**

Basis of dose selection: Not provided

Negative controls: Direct Culture medium

Metoclopramide concentrations used: 1.0, 1.8 and 3.2 mM

Positive control: Ethylmethane sulfonate (EMS)

Cell Line Used: V79 Chinese hamster lung cells TG resistance - TG^r

Results:

20-Hr exposure of metoclopramide to cells in the absence of metabolic activation produced increased number TG resistant clones, from 3 to 7.8 times the control group at 3.2 mM concentration. The increase in the number of TG resistant clones at 1.0 and 1.8 mM were similar to the control cultures. The number of mutant colonies in the assay #3 was much higher due to the cytotoxicity (the relative cell survival reduced to 0.29) and the results are shown in the table 3 of the publication (vol 8:12, pp 068):

Metoclopramide induced an increased number of TG resistant mutant frequency and was mutagenic in hypoxanthine guanine phosphoribosyl transferase (HGPRT) mutation assay.

(iv) **Induction of micronuclei in Human lymphocytes**

Basis of dose selection: Not provided

Negative controls: Direct Culture medium

Metoclopramide concentrations used: 0.1, 0.32 and 1.00 mM (28 hr and, 0, 0.1 and 1.0 mM for 72 hr)

Results:

Metoclopromide did not induce the micronuclei at 28 hr exposure but a dose related significant increase in mononucleated and binucleated micronuclei were seen at 1.0 mM concentration in 72 hr exposure assay. The results showed metoclopramide induce an increase in micronuclei in cytokinesis-blocked human lymphocytes. The data is shown below in table #4 (sponsor vol 8:12, pp 069):

TABLE 4
Induction of Micronuclei in Cytokinesis-Blocked Human Lymphocytes Following Exposure to MCA or PCA

Compound	Concn (mM)	Donor No	BN (% ± SD)	MnMN (‰ ± SD)	MnBN (‰ ± SD)
			28-hr treatment		
MCA	0	1	40.5 ± 11.0	7.5 ± 6.5	32.5 ± 24.3
	0.10		41.2 ± 3.3	13.2 ± 9.8	39.8 ± 17.4
	0.32		39.8 ± 25.2	10.6 ± 7.0	37.4 ± 23.2
	1.00		57.7 ± 14.3	11.2 ± 9.7	30.3 ± 5.7
MCA	0	2	33.7 ± 2.3	8.4 ± 1.2	8.4 ± 2.3
	0.10		28.6 ± 6.7	4.0 ± 3.2	14.6 ± 3.4
	0.32		25.4 ± 5.4	3.9 ± 3.5	18.9 ± 10.0
	1.00		33.8 ± 14.4	2.5 ± 2.4	5.2 ± 5.3
PCA	0	3	30.0 ± 13.5	0.8 ± 1.1	3.5 ± 2.0
	0.10		25.8 ± 7.9	1.6 ± 1.8	4.2 ± 3.1
	0.32		41.9 ± 2.1	0	1.8 ± 1.6
	1.00		33.0 ± 5.6	0	3.8 ± 1.4
			72-hr treatment		
MCA	0	4	23.7 ± 7.7	14.0 ± 16.4	42.5 ± 5.9
	0.10		39.8 ± 8.2	29.2 ± 0.5*	74.9 ± 36.0*
	1.00		36.5 ± 24.2	42.5 ± 32.5***	116.1 ± 42.7***
MCA	0	5	35.8 ± 7.5	3.1 ± 4.7	5.5 ± 4.9
	0.10		24.6 ± 5.3	2.9 ± 2.5	5.9 ± 5.1
	0.32		32.8 ± 3.4	4.6 ± 4.6	3.7 ± 2.9
	1.00		27.4 ± 2.8	8.0 ± 0.4*	21.1 ± 10.6**
PCA	0	6	48.7 ± 12.6	0.9 ± 1.5	6.9 ± 6.2
	0.10		49.7 ± 13.5	2.4 ± 3.0	4.6 ± 5.3
	0.32		39.6 ± 5.6	0	1.5 ± 2.5
	1.00		41.8 ± 10.4	1.3 ± 2.7	10.5 ± 8.5

Note Abbreviations used: BN, binucleated cells; MnMN, micronucleated mononucleated cells; MnBN, micronucleated binucleated cells. Values are the means of counts performed on triplicate cultures scoring 1500 binucleated lymphocytes. Statistical significance of the difference from corresponding control values was evaluated according to the method for comparison of two percentages based on two large samples described by Bailey (1959): $^*p < 0.02$; $^{**}p < 0.01$; $^{***}p < 0.001$.

In summary, metoclopramide induced an increase in the frequency of mutation frequency at the *hgprt* locus in V79 Chinese hamster lung cells and it was clastogenic in micronucleus test using human lymphocytes.

2.6.6.4.2 Study title: Evaluation of (i) DNA-Damaging activity, (ii) Clastogenic activity and (iii) Tumor Promoting Activity of Metoclopramide and Procainamide in Rats. Mereto, E., Robbiano, L et al, Toxicol & Applied Pharmacol. 131: 192-197, 1995

Key findings: Metoclopramide was a tumor promoting agent in the test.

The data of each of the parameters were separated and reviewed below:

(i) **Determination of DNA-Damaging Potential of Metoclopramide and Procainamide in Rats.**

Conducting laboratory and location: Institute of Pharamcology, University of Geoa, Italy

Methods

Strains/species/cell line: SD rats (100-150 g) S.Polo d'Enza, Italy

Doses used in definitive study: 500 mg/kg in a volume of 10 ml/kg in water.

Basis of dose selection: The dose was selected on the LD_{50} close to the identified dose of 647 mg/kg in rats (NOISH, 1987).

Negative controls: 0.5% carboxymethylcellulose in water

Positive controls: N-methyl-N-nitro-N-nitrosoguanidine (MNNG), N-nitrosodiethylamine (NDEA) and 2-acetylaminofluorene (2-AAF) and cyclophosphamide (CP)

Randomly bred male SD fasted rats were treated with 500 mg/kg metoclopramide, sacrificed after 3 hr of treatment and liver, kidneys, stomach, spleen and bone marrow separated. The amount of DNA fragmentation (Ki/Kc) in each sample was evaluated by comparing the DNA elution rate of the treated and control rate by the procedure of Cesarone et al (1979).

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The single dose of 1.2 mg/kg, ip NDMA in liver induced an increase in the relative elution rate in the liver and, a single dose of 26 mg/kg, ip NDMA and 250 mg/kg MNNG also

induced an increase in the relative elution rate in gastric mucosa but no DNA fragmentation. A dose of 80 mg/kg ip phosphamide induced DNA fragmentation in the bone marrow.

DNA-Damaging Activities:

A single dose of 500 mg/kg po metoclopramide did not cause DNA fragmentation in liver, kidneys, stomach, spleen and bone marrow of the animals as shown in sponsor's submission (table in vol 1.8, table 1, pp 073).

TABLE 1
DNA Fragmentation in Some Tissues of Sprague-Dawley Male Rats after Single po Administration of MCA and PCA

Tissue	Treatment conditions (mg/kg)	No. of rats	K_r/K_c[a] (mean ± SD)
Liver	Control	6	(K_c = 0.0154 ± 0.0025)
	MCA (500)	6	1.01 ± 0.03
	PCA (500)	5	1.16 ± 0.07
	NDMA (1.2)	4	1.92 ± 0.14*
Kidney	Control	4	(K_c = 0.0207 ± 0.0016)
	MCA (500)	4	1.01 ± 0.01
	PCA (500)	4	1.10 ± 0.02
	NDMA (26)	4	1.86 ± 0.13*
Gastric mucosa	Control	4	(K_c = 0.0329 ± 0.0036)
	MCA (500)	4	1.04 ± 0.03
	PCA (500)	4	1.03 ± 0.03
	MNNG (250)	4	2.66 ± 0.16*
Spleen	Control	4	(K_c = 0.0159 ± 0.0016)
	MCA (500)	4	1.12 ± 0.04
	PCA (500)	4	1.08 ± 0.03
	CP (80)	4	2.09 ± 0.14*
Bone marrow	Control	4	(K_c = 0.0170 ± 0.0017)
	MCA (500)	4	1.09 ± 0.08
	PCA (500)	4	1.07 ± 0.06
	CP (80)	4	1.78 ± 0.13*

[a] Relative DNA elution rate calculated as described under Materials and Methods
* $p < 0.05$; statistical significance of the increase in DNA elution rate versus corresponding controls was calculated by means of the Wilcoxon two-sample (two-tailed) test (Rünke and De Jonge, 1964).

Metoclopramide did not induce DNA fragmentation in the tissues of treated rats.

(ii) **Clastogenic Activity:**

Induction of Micronulei by Metoclopramide and Procainamide in Rat Hepatocytes and Bone Marrow.

Conducting laboratory and location: Institute of Pharmacology, University of Geoa, Italy

Methods

Strains/species/cell line: SD rats (100-150 g) S.Polo d'Enza, Italy

Doses used in definitive study: 500 mg/kg in a volume of 10 ml/kg in water.

Basis of dose selection: The dose was close to the identified LD_{50} dose of 647 mg/kg in rats (NOISH, 1987).

Negative controls: 0.5% carboxymethylcellulose in water

Positive controls: N-methyl-N-nitro-N-nitrosoguanidine (MNNG), N-nitrosodiethylamine (NDEA) and 2-acetylaminofluorene (2-AAF) and cyclophosphamide (CP)

The increase in the micronuclei frequency in hepatocytes was evaluated by the procedure of Tates et al (1980) and the frequency in bone marrow preparations of the rat was evaluated after 48 hr treatment period.

Results:

No significant increase in the frequency of the micronucleated hepatocytes was seen in rats treated for 48 hr with 500 mg/kg metoclopramide. The frequency of MNPCEs in the bone marrow PCEs was also not noted. The increase in the frequency of bi-nucleated hepatocytes and mitotic index were not seen, metoclopramide might not be capable of retarding heptacellular regeneration. NDMA at 10 mg/kg (a positive control) induced micronuclei in hepatocytes and bone marrow erythrocytes. The data is shown in sponsor's vol 1.8, table 2, pp 73:

TABLE 2
Frequency of Micronucleated Hepatocytes in Rats Treated with a Single po Dose of MCA and PCA

Treatment conditions (mg/kg)	No. of hepatocytes observed	Frequency of micronucleated hepatocytes (‰ ± SD)	Frequency of binucleated hepatocytes (‰ ± SD)	Mitotic index (‰ ± SD)
Control	5023	1.39 ± 0.89	65.0 ± 56.4	15.0 ± 7.9
MCA (500)	5116	1.94 ± 1.17	88.7 ± 30.1	8.9 ± 5.1
PCA (500)	5337	1.65 ± 0.60	45.7 ± 18.1	11.9 ± 8.2
NDMA (10)	3015	6.30 ± 2.22*	60.7 ± 17.4	19.9 ± 14.6

Note. The control group, the MCA group, and the PCA group consisted of five rats, the NDMA group consisted of three rats. The values are the means of individual rat data.

* $p < 0.05$ versus controls according to the Wilcoxon two-sample (two-tailed) test (Runzke and De Jonge, 1964).

Metoclopramide did not induce significant increase the frequency of micronucleated hepatcytes or micronucleated polychromatic erythrocytes in bone marrow cells.

(iii) **Tumor Promoting Activity**:
Determination of Tumor Promoting Activity of Metoclopramide and Procainamide in Rats.

Conducting laboratory and location: Institute of Pharmacology, University of Geoa, Italy

Methods

Strains/species/cell line: SD rats (100-150 g) S.Polo d'Enza, Italy

Doses used in definitive study: 500 mg/kg in a volume of 10 ml/kg in water.

Basis of dose selection: The dose was selected on the LD_{50} close to the identified dose of 647 mg/kg in rats (NOISH, 1987).

Negative controls: 0.5% carboxymethylcellulose in water

Positive controls: N-methyl-N-nitro-N-nitrosoguanidine (MNNG), N-nitrosodiethylamine (NDEA) and 2-acetylaminofluorene (2-AAF) and cyclophosphamide (CP)

The liver hyperplastic foci were determined by using Solt-Faber assay in 3 groups of SD rats treated with NDMA (200 mg/kg, ip). One of the group (4-6 /group) of the treated animals were treated with a dose of 500 mg/kg/day metoclopramide and the other groups were treated with vehicle and positive control, cyclophosphamide for 2 weeks. The animals were subjected to partial hepatotomy after 1 week of hepatocyte induction. On day 28, animals sacrificed and liver removed, 2 um sections cut and the ice cold sections were embedded in paraffin and 5um thick section were stained for γ-glutamethyltransferase (GGT). The other sections were stained with hematoxylin-eosin. GGT positive and basophilic foci were estimated with an automatic image analyzer. The # of foci/cm^3 was calculated by Campbell et al. (Cancer Res. 42: 465-72, 1979).

Results:

The 2-week treatment with 0.125% metoclopramide solution in water produced a significant increase in the rat body and liver weights. The number of areas and diameters of GGT positive and basophilic foci in hepatocytes were increased in a significant manner by metoclopramide and 2-AAF in rats initiated with NDEA-treated rats. The 2-AAF and metoclopramide treatment in these NDEA treated rats increased the number of foci by 2.8 and 4.3 times, respectively and the increase in size (area) was 38 and 9.1 times in 2-AAF and metoclopramide treated rats. The metoclopramide treatment produced an increased number and size of liver hyperplastic foci in rats as shown in table 4 of the research publication (vol. 1.8, pp. 074).

TABLE 4 Increase in Body Weight, Liver Weight, and GGT-Positive and Basophilic Foci Quantitation in Rats Initiated with NDEA and Subsequently Given MCA, PCA, or 2-AAF for 2 Weeks According to the Solt-Farber Assay (Means ± SD)

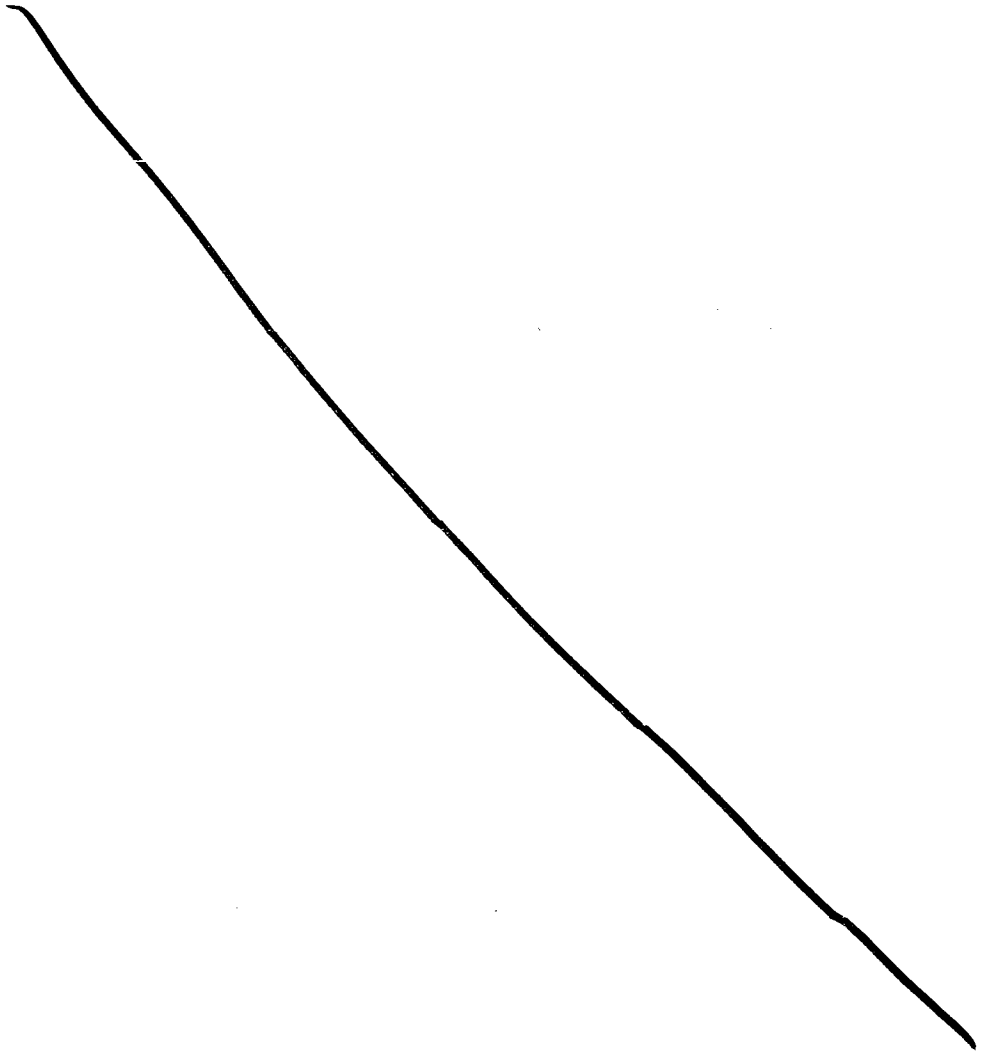
Group	Treatment Conditions	No. of rats	Average intake per rat (mg/kg/day)	Increase in body weight (g)	liver weight (% of body weight)	Type of foci	No. of foci /crn^2	No. of foci /cm^3	Average diameter (um)	Area (mm'/cm^2)
1	NDEA + MCA (0.125% in drinking water)	12	260 ± 10	51 ± 39[b]	3.9 ± 054[d]	GGT*	43.1 ± 35.5[e]	1713 ±1276[e]	178± 49[e]	1.18±1.12[e]
						Basophilic	4.0 ± 4.3[f]	89 ±118[f]	334 ±133[e]	0.42±0.47[f]
2	NDEA + PCA (0.125% in drinking water)	12	235 ± 22	166 ± 17[b]	3.9 ± 0.3[c]	GGT*	15.2 ±11.6[g]	650 ± 493	161 ± 40	0.32±0.24[f]
						Basophilic	3.1 ±4.6	94 ± 152	246:t 56	0.12 ±0.16
3	NDEA + 2-AAF (0.02% in the diet)	8	16 ± 2	29 ± 14[b]	2.7 ± 0.5[b]	GGT*	50.2±21.0	1132±459[e]	313 :t 128[b]	4.94±3.23[e]
						Basophilic	61.0 ± 20.1[e]	1627±419[f]	264 ± 105	4.15±3.09[e]

4	NDEA	22	-	90 ± 28	3.6 ± 0.3	GGT*	8.1 ± 7.0	401± 320	137 ± 35	0.3 ± 0.10
						Basophilic	0.8 ± 1.4	20± 39	225± 58	0.04 ±0.08

[a] The initiating dose of NDEA was 200 mg ip.
[b,c,d,e] Significantly different from control group (group 4) as calculated by means of the Student's *t* test (two-tailed): [b] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$. [e,f,g] Significantly different from control group (group 4) as calculated by means of the Mann-Whitney two-sample (two-tailed) test [e] $p < 0.001$; [f] $p < 0.01$; [g] $p < 0.05$.

Study outcome: The treatment with metoclopramide for 14 days induced an increase in the number of hepatic foci and their size (area) indicating that it has tumor promoting potential.

2.6.6.6 LABELING:



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✓ Draft Labeling

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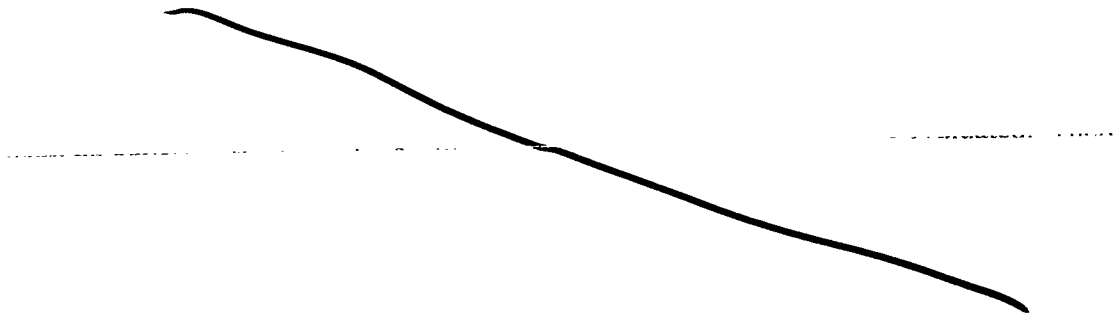
Withheld Track Number: Pharm/Tox- 2



OVERALL CONCLUSIONS AND RECOMMENDATIONS

The oral rapid disintegrating tablet (ODT) is solubilized in the mouth and releases its contents, which is swallowed with or without water. The formulation of the tablets contains an increased amount of disintegrating agent and the tablets prepared under low compact pressure and this provides more porosities to release metoclopramide rather fast. Metoclopramide acts by increasing the gastrointestinal motility by inhibiting dopaminergic mechanisms and thus manifest the unopposed central cholinergic activity. This leads to an increased release of acetylcholine from enteric neurons, suppress the interneurons by the antagonism of 5-HT_3 receptors and stimulation of excitatory neurons via 5-HT_4 receptors.

Sponsor did not submit any new preclinical pharmacology studies with the rapid disintegrating tablets with the present application but relied on the information submitted with NDA 17-854 (metoclopramide tablets). In the pharmacology review of NDA 17-854 (metocopramide tablet), the studies reviewed were: the pharmacodynamic studies, ADME studies on the absorption of orally administered compound in dog, rabbit, mouse and man, absorption of intramuscularly administered compound in rabbit, absorption of subcutaneously administered compound rabbit and rats, tissue/plasma distribution of a single oral/sc dose in rats and mice, metabolism and excretion study in rats, dogs and rabbits, acute toxicity studies in adult and young rats by oral and subcutaneous route, 2- and 5- week toxicity studies by intramuscular and intravenous routes in rats and dogs, 77-week oral study in rats, 16-week oral and subcutaneous toxicity study in dogs, 54-week chronic oral toxicity study in dogs, oral segment II Teratology studies in rats and rabbits, perinatal and postnatal toxicity study in rats, segment II Teratology studies in Watanabe rats, mice and rabbits, special rectal irritation study in rabbits and dogs, interaction study in rats. Sponsor in the present submission had shown that metoclopramide ODT in healthy volunteers was bioequivalent to the currently marketed metoclopramide hydrochloride immediate release (IR) 10 mg oral tablet (swallowed with 240 ml water) under fasting conditions. The plasma concentrations ($AUC_{0\text{-}infin}$ values) were 357$\pm$147 ng.hr/ml and 368$\pm$136 ng.hr/ml by the proposed 10-mg ODT and 10 mg currently marketed metoclopramide tablet, respectively.

The orally administered metoclopramide was rapidly absorbed, bound up to 20 to 30% to plasma proteins and 80% of the radioactivity administered with the tagged compound was excreted in urine in about 72 hr. The absolute bioavailability of the orally administered compound was 80% and half of it was reported to be present as conjugated compound in the plasma.

In the present application, the sponsor submitted 2 research publications for determining the genotoxicity potential of metoclopramide. In one study for the evaluation of DNA-damaging and promoting clastogenic activities in rats, metoclopramide at a concentration of 3.2 mM (1133.8 mg concentration) induced an increase in the frequency of mutation frequency at the *hgprt* locus in V79 Chinese hamster lung cells and it induced an increase in the number of micronuclei in human lymphocytes. This concentration was 39096 and 19961 times the concentration of 29 and 56.8 ug/l achieved by the first and 10^{th} dose of 0.15 mg/kg in a man.

In the second study on the 'evaluation of DNA-damaging, clastogenic and tumor promoting activities of metoclopramide and procainamide in rats', metoclopramide at a single dose of 500 mg/kg po (3000 mg/m^2) metoclopramide did not produce DNA fragmentation but in rats initiated with N-nitroso dimethylamine (200 mg/kg, ip NDEA), a treatment with metoclopramide caused an increased size and greater number of GGT-positive and basophilic foci. Metoclopramide was assessed to have tumor promoting effect in rats.

The changes suggested in the text of the present review should be inserted in the proposed label.

RECOMMENDATIONS:

1. The proposed application approval from the preclinical standpoint is recommended.

2. The sponsor should change the proposed label as described under the labeling section of the review.

Yash M. Chopra
Pharmacologist, HFD-180

COMMENTS:

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

cc:Original NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chopra
HFD-180/Dr. Choudary
HFD- /Dr. Viswanathan

R/D Init.: J. Choudary 5/3/05

YC: NDA 21793cd.doc/5/20/05

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/s/

Yash Chopra
5/20/05 06:09:18 PM
PHARMACOLOGIST

Jasti Choudary
5/22/05 04:33:23 PM
PHARMACOLOGIST
A supervisory addendum for corrections in the review and for final labeling recommendations will follow.

There is no CAC report for this NDA.