

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-246

PHARMACOLOGY REVIEW(S)

**PHARMACOLOGIST'S REVIEW OF NDA 22-246
(Class 2 Resubmission dated March 10, 2009)**

Sponsor: Wilmington Pharmaceuticals, LLC
Wilmington, NC

Reviewer: Tamal K. Chakraborti, Ph.D.
Pharmacologist, DGP

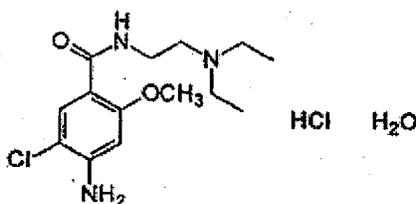
Date of Submission: March 10, 2009

Date of Receipt: March 11, 2009

Date of Review: June 12, 2009

Drug: Metozolv ODT (Metoclopramide Orally Disintegrating Tablets), 5 mg and 10 mg

Structure:



Category: Antiemetic/prokinetic/dopamine receptor antagonist

Indication: Metozolv ODT is indicated for the treatment of symptomatic gastroesophageal reflux disease (GERD) and diabetic gastroparesis (diabetic gastric stasis).

Submission Contents: Complete Response (CR)

Background: This submission is in reference to January 29, 2008 Original NDA for Metozolv ODT. The Agency issued a CR letter dated February 26, 2009, which stated that NDA 22-246 could not be approved in its present form. The sponsor was asked to submit a Risk Evaluation and Mitigation Strategy (REMS) with a Medication Guide, revised draft labeling, a revised stability commitment, and a safety update. For safety update, the sponsor was asked to include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level. This resubmission is a complete response to the CR letter dated February 26, 2009.

SUMMARY AND EVALUATION:

The sponsor did not submit any new nonclinical study reports or information in this submission. The sponsor stated that no new adverse events, serious adverse events, adverse events resulting in study withdrawal, or deaths; and no new exposure data for Metozolv ODT have been collected or analyzed from nonclinical studies or from clinical studies since NDA 22-246 resubmission on January 29, 2008. Please refer to pharmacology review of Original NDA 22-246 dated October 1, 2008 for nonclinical review.

RECOMMENDATIONS: None.

_____ Tamal K. Chakraborti, Ph.D. Pharmacologist, DGP	_____ Date
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Comment:

_____ Sushanta K. Chakder, Ph.D. Supervisory Pharmacologist, DGP	_____ Date
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this page is the manifestation of the electronic signature.**

/s/

Tamal Chakraborti
6/12/2009 03:06:31 PM
PHARMACOLOGIST

Sushanta Chakder
6/12/2009 03:50:47 PM
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:	22-246
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	1/30/08
PRODUCT:	Metozolv ODT (Metoclopramide Orally Disintegrating Tablets)
INTENDED CLINICAL POPULATION:	Patients with GERD or diabetic gastroparesis
SPONSOR:	Wilmington Pharmaceuticals, LLC
DOCUMENTS REVIEWED:	N/A [505(b)(2) Application]
REVIEW DIVISION:	Division of Gastroenterology Products (DGP)
PHARM/TOX REVIEWER:	Tamal K. Chakraborti, Ph.D.
PHARM/TOX ACTING TEAM LEADER:	David B. Joseph, Ph.D.
DIVISION DIRECTOR:	Donna Griebel, M.D.
PROJECT MANAGER:	Maureen Dewey, MPH

Date of review submission to Division File System (DFS): September 25, 2008

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EXECUTIVE SUMMARY

I. Recommendations:

A. Recommendation on Approvability: From a nonclinical standpoint, this NDA is recommended for approval for the proposed use.

B. Recommendation for Nonclinical Studies: None

C. Recommendations on Labeling: Metoclopramide is recommended for the treatment of symptomatic gastroesophageal reflux as short term (4 to 12 weeks) therapy for adults with symptomatic gastroesophageal reflux who fail to respond to conventional therapy (10 to 15 mg orally up to four times daily) and diabetic gastroparesis (diabetic gastric stasis) for two to eight weeks (10 mg four times daily). The draft labeling of Metozolv generally conforms to the format specified under 21CFR 201.57(c)(14) Requirements for PLR (Physician's Labeling Rule) Prescription Drug Labeling. However, the following changes should be incorporated.

8.1 Pregnancy

Sponsor's Version:

(b) (4)

Evaluation: The text is in accordance with 21CFR 201.57(c)(14). However, the labeling text should be modified as proposed below.

Recommended Version:

"8.1 Pregnancy

Teratogenic effects: Pregnancy Category B

Reproduction studies have been performed in rats at oral doses (b) (4) (about 6 times the maximum recommended human oral dose based on body surface area) and in rabbits at oral doses (b) (4) (about 12 times the maximum recommended human oral dose based on body surface area) 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.”

8.3. Nursing Mothers

Sponsor’s Version

(b) (4)

Evaluation: The text is in accordance with 21CFR 201.57(c)(14). However, the text should be changed to make it concordant with the “Nursing Mothers” section of the Reglan ODT labeling.

Recommended Version:

“8.3 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 (b) (4), 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.”

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor’s Version

(b) (4)

(b) (4)



Evaluation: The text is in accordance with 21CFR 201.57(c)(14)(i). However, the text should be modified as proposed below.

Recommended Version:**“Carcinogenesis, Mutagenesis, Impairment of Fertility**

A 77-week study was conducted in rats with oral doses up to 40 mg/kg/day (about 5 times the maximum recommended human dose based on body surface area).

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 based on body surface area) 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 (about 3 times the maximum recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.”

II. Summary of Nonclinical Findings:

- A. **Brief Overview of Nonclinical Findings:** The sponsor did not submit any non-clinical study reports in this NDA. Instead, the sponsor made the following statement: “The Zydis[®] ODT development program did not include nonclinical studies since the sponsor is relying on the Agency's previous findings of safety and efficacy for reference list drug (RD), Reglan[®] Tablets and that there is no difference in the strength, dose, route of administration, clinical indication, or duration of dosing.” Metoclopramide toxicity has been adequately characterized in toxicology studies conducted by the innovator (NDA 17,854 and NDA 21,793). In repeat-dose toxicology studies in rats, the target organs appeared to be the mammary glands (increased secretion and

increased development of ducts and acinar tissue) and liver (elevation of liver enzymes). In dogs, the CNS (decreased activity, vocalization, chewing, tremors and hyperthermia) appeared to be the target organ.

- B. Pharmacologic Activity: Metoclopramide is a dopamine D₂ receptor antagonist and is also a mixed 5- hydroxytryptamine (5-HT₃) receptor antagonist/5-HT₄ receptor agonist. In the upper GI tract, metoclopramide increases both acetylcholine (ACh) release from neurons and cholinergic receptor sensitivity to ACh. Metoclopramide stimulates and coordinates esophageal, gastric, pyloric, and duodenal motor activity. It increases lower esophageal sphincter tone and stimulates gastric contractions, while relaxing the pylorus and duodenum. Inadequate cholinergic activity may play a key role in many GI motility disorders. Therefore, metoclopramide is expected to be effective in motility disorders. Metoclopramide increases gastric emptying of liquids, but may decrease the emptying of solids. It has little or no effect on colonic motility. Metoclopramide readily crosses the blood-brain barrier, where dopamine (DA) antagonism at the chemoreceptor trigger zone (CTZ) produces an antiemetic effect. However, dopamine antagonism in the brain causes adverse effects collectively known as extrapyramidal symptoms, which include acute dystonic reactions, Parkinsonian-like symptoms, and tardive dyskinesia.
- C. Nonclinical Safety Issues Relevant to Clinical Use: None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-246

Review number: 001

Sequence number/date/type of submission: 000/Januray 29, 2008/Original

Information to sponsor: Yes (X) No ()

Sponsor: Wilmington Pharmaceuticals, LLC, Wilmington, NC

Manufacturer for drug substance: (b) (4)

Reviewer name: Tamal K. Chakraborti, Ph.D.

Division name: Division of Gastroenterology Products (DGP)

Review completion date:

Drug:

Trade name: Metozolv ODT (Metoclopramide Orally Disintegrating Tablets),
5 mg and 10 mg

Generic name: Metoclopramide

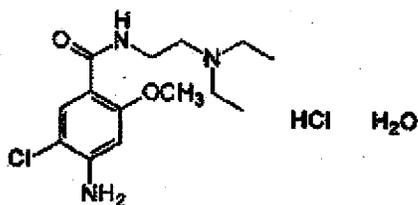
Code name: None

Chemical name: 2-Methoxy-4-amino-5-chloro-N,N
dimethylaminoethyl)benzamide monohydrochloride monohydrate

CAS registry number: 54143-57-6

Molecular formula/molecular weight: C₁₄H₂₂ClN₃O₂•HCl.H₂O/354.3

Structure:



Relevant INDs/NDAs:

1. IND 70,578 (Zydis[®] Orally Disintegrating Tablets (ODT), 5 mg and 10 mg, Wilmington Pharmaceuticals, LLC)
2. NDA 17-854 (Reglan[®] Tablets, Schwarz Pharma)
3. NDA 21-793 (Reglan[®] ODT, Schwarz Pharma)

Drug class: antiemetic/prokinetic/dopamine receptor antagonist

Intended clinical population: Metoclopramide Orally Disintegrating Tablets is indicated for the treatment of symptomatic gastroesophageal reflux disease (GERD) and diabetic gastroparesis (diabetic gastric stasis).

Clinical formulation: The following table (from page 230 of sponsor’s submission) shows the formulation.

Table 2.3-8: Composition of the Drug Product

Component/Quality	Function	Quantity per 5 mg Tablet	Quantity per 10 mg Tablet	Amount (%w/w) per dried tablet
Metoclopramide HCl, USP (as free base)	Active	5.00 mg ¹	10.00 mg ¹	(b) (4)
Gelatin, NF				(b) (4)
Mannitol, USP				
Mint Flavor				
(b) (4)				
Acesulfame Potassium, NF				
(b) (4)				
Sodium Hydroxide, NF ³				
Total				

Route of administration: Oral

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

Data reliance : Any information or data necessary for approval of NDA 22-246 that Wilmington Pharmaceuticals, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that Wilmington Pharmaceuticals, LLC does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-246.

Studies reviewed within this submission: This NDA was submitted as a 505 (b)(2) application. The sponsor did not conduct any nonclinical studies with metoclopramide. The sponsor made the following statement.

“The Zydys[®] ODT development program did not include nonclinical studies since the sponsor is relying on the Agency's previous findings of safety and efficacy for reference list drug (RD), Reglan[®] Tablets and that there is no difference in the strength, dose, route of administration, clinical indication, or duration of dosing. The Agency agreed to this approach at the November 4, 2004 pre- IND 70,578 meeting but noted the NDA should contain a full evaluation of all safety information to date and include copies of any full report that were available. The nonclinical written and tabulated summaries that follow are a compilation of data from the Summary Basis of Approval (SBA) documents for the approved application, Reglan[®] Tablets (NDA 17,854; approved December 30, 1980), as well as published articles. The SBA for Reglan[®] ODT (NDA 21,793; approved June 6, 2005) does not include any additional data to be relied upon. NDA 21,793 only references published report of additional data submitted in NDA 17,854, which are likewise cited herein.”

Studies not reviewed within this submission: Not applicable.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Metoclopramide is a dopamine D₂ receptor antagonist and is also a mixed 5-hydroxytryptamine (5-HT₃) receptor antagonist/5-HT₄ receptor agonist. In the upper GI tract, metoclopramide increases both acetylcholine (ACh) release from neurons and cholinergic receptor sensitivity to ACh. Metoclopramide stimulates and coordinates esophageal, gastric, pyloric, and duodenal motor activity. It increases lower esophageal sphincter tone and stimulates gastric contractions, while relaxing the pylorus and duodenum. Inadequate cholinergic activity may play a key role in many GI motility disorders. Therefore, metoclopramide is expected to be effective in motility disorders. Metoclopramide increases gastric emptying of liquids, but may decrease the emptying of solids. It has little or no effect on colonic motility. Metoclopramide readily crosses the blood-brain barrier, where dopamine (DA) antagonism at the chemoreceptor trigger zone (CTZ) produces an antiemetic effect. However, dopamine antagonism in the brain causes adverse effects collectively known as extrapyramidal symptoms, which include acute dystonic reactions, Parkinsonian-like symptoms and tardive dyskinesia.

2.6.2.2 Primary pharmacodynamics

No studies were conducted.

2.6.2.3 Secondary pharmacodynamics

No studies were conducted.

2.6.2.4 Safety pharmacology

No studies were conducted.

2.6.2.5 Pharmacodynamic drug interactions

No studies were conducted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS**2.6.4.1 Brief summary**

The pharmacokinetic (PK) profile was studied in rodents, rabbits, and dogs. Metoclopramide was well absorbed from the gastrointestinal (GI) tract following oral administration in mice, rats, dogs, rabbits and humans. The percent of oral dose recovered from the urine in rats and dogs was 80% and 73% at 24 hours post-dose, respectively. The plasma half-life of orally or parenterally administered drug varied from one to three hours. Metoclopramide was bound to non-dialyzable constituents of the plasma to an extent of 13-22%. Metoclopramide was distributed to most tissues but concentrated particularly in the kidney, liver, heart, adrenal, and thymus. In mice and rats, metoclopramide was distributed to the brain following either oral or parenteral administration. Tissue levels were comparatively low at 24 hours post-dose. In rats, dogs, and rabbits, metoclopramide was partially metabolized to five or six different metabolites. The most common metabolites in the rat and dog were N-monodeethylated form and a hippuric acid derivative. In rats and dogs, a significant portion of the administered dose was eliminated in the urine as unchanged drug (30-40% of urinary content). Urinary excretion was the major route of elimination, accounting for about 73% of an oral dose in dogs and about 82% of an oral dose in rats. The drug was completely excreted by 24 hours. Biliary excretion accounted for approximately 2% of the total dose.

2.6.4.2 Methods of Analysis

No studies were conducted.

2.6.4.3 Absorption

No studies were conducted.

2.6.4.4 Distribution

No studies were conducted.

2.6.4.5 Metabolism

No studies were conducted.

2.6.4.6 Excretion

No studies were conducted.

2.6.4.7 Pharmacokinetic drug interactions

No studies were conducted.

2.6.4.8 Other Pharmacokinetic Studies

No studies were conducted.

2.6.4.9 Discussion and Conclusions

The pharmacokinetics of metoclopramide have been studied in rodents (mice and rats), rabbits, dogs, and humans. Metoclopramide was well absorbed from the GI tract following oral administration and distributed into various tissues and organs such as the liver, kidney, heart and brain. Although N-deethylation was observed as a major pathway in animals, there were no reports of that metabolic route in humans. Hepatic metabolism of metoclopramide is primarily mediated through CYP2D6.

2.6.4.10 Tables and figures

Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable.

2.6.6 TOXICOLOGY**2.6.6.1 Overall toxicology summary**

General toxicology: The sponsor did not conduct any nonclinical studies. In repeat-dose toxicology studies in rats, the target organs of toxicity appeared to be the mammary glands (increased secretion and increased development of ducts and acinar tissue) and the liver (elevation of liver enzymes). In dogs, the CNS (decreased activity, vocalization, chewing, tremors and hypothermia) appeared to be the target organ. As recommended, the sponsor conducted a search of four large databases (Medline, Derwent Drug Files, Biosis and Embase) from 1997 to 2007. No new information was identified in any publication that would significantly impact the labeling of Metozolv.

Genetic toxicology: Metoclopramide was negative in the Ames test, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat and human hepatocytes, and the *in vivo* rat micronucleus assay. However, metoclopramide was positive in the *in vitro* Chinese hamster lung cell /HGPRT forward mutation assay and the *in vitro* human lymphocyte chromosome aberration assay. The sponsor presented (on page 307 of the NDA) a published report from the European Environmental Mutagen Society [Copenhagen, Denmark, 1999 by Lafouge P et al. (Metoclopramide: Absence of genotoxic potential following the basic ICH battery of tests. *Pharmacol Toxicol* 1999;85 (Suppl. 1):56] that described evaluation of genotoxicity using the Ames test, mouse lymphoma assay, and mouse micronucleus test. In this report, metoclopramide was found to be negative in the Ames test, mouse lymphoma assay, and mouse micronucleus test.

Carcinogenicity: 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.

Reproductive toxicology: 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. The sponsor presented findings from a recently published study in mice that indicated that metoclopramide-induced hyperprolactinemia may have suppressive effects on ovarian function and may have a negative impact on mouse embryo implantation (Panzan MQ et al. Metoclopramide-induced hyperprolactinaemia caused marked decline in pinopodes and pregnancy rates in mice. *Hum Reprod* 2006;2:2514-20).

Special toxicology: None.

2.6.6.2 Single-dose toxicity

No studies were conducted.

2.6.6.3 Repeat-dose toxicity

No studies were conducted.

2.6.6.4 Genetic toxicology

No studies were conducted.

2.6.6.5 Carcinogenicity

No studies were conducted.

2.6.6.6 Reproductive and developmental toxicology

No studies were conducted.

2.6.6.7 Local tolerance

No studies were conducted.

2.6.6.8 Special toxicology studies

No studies were conducted.

2.6.6.9 Discussion and Conclusions

This NDA was submitted as a 505 (b)(2) application. The sponsor did not conduct any nonclinical studies with metoclopramide. The sponsor is relying on the Agency's previous findings of safety and efficacy for the reference listed drug (RLD), Reglan® Tablets. There is no difference in the strength, dose, route of administration, clinical indication, or duration of dosing of Reglan Tablets and Metozolv ODT.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Metoclopramide is a dopamine D₂ receptor antagonist and is also a mixed 5-hydroxytryptamine (5-HT₃) receptor antagonist/5-HT₄ receptor agonist. The anti-emetic action of metoclopramide is considered to be due to its antagonist activity at D₂ receptors in the chemoreceptor trigger zone (CTZ) in the CNS. The prokinetic activity of metoclopramide is considered to be mediated by muscarinic activity, D₂ receptor antagonist activity, and 5-HT₄ receptor agonist activity. Reglan is indicated for the treatment of symptomatic gastroesophageal reflux disease (GERD) and diabetic gastroparesis. This NDA was submitted as a 505 (b)(2) application. The sponsor did not conduct any nonclinical studies with metoclopramide. Instead, the sponsor provided the following statement: "The Zydis[®] ODT development program did not include nonclinical studies since the sponsor is relying on the Agency's previous findings of safety and efficacy for reference list drug (RD), Reglan[®] Tablets and that there is no difference in the strength, dose, route of administration, clinical indication, or duration of dosing."

In the upper GI tract, metoclopramide increases both acetylcholine (ACh) release from neurons and cholinergic receptor sensitivity to ACh. Metoclopramide stimulates and coordinates esophageal, gastric, pyloric, and duodenal motor activity. It increases lower esophageal sphincter tone and stimulates gastric contractions, while relaxing the pylorus and duodenum. Inadequate cholinergic activity may play a key role in many GI motility disorders. Therefore, metoclopramide is expected to be effective in motility disorders. Metoclopramide increases gastric emptying of liquids, but may decrease the emptying of solids. It has little or no effect on colonic motility. Metoclopramide readily crosses the blood-brain barrier, where dopamine (DA) antagonism at the chemoreceptor trigger zone (CTZ) produces an antiemetic effect. However, dopamine antagonism in the brain causes adverse effects collectively known as extrapyramidal symptoms, which include acute dystonic reactions, Parkinsonian-like symptoms, and tardive dyskinesia.

The pharmacokinetic (PK) profile was studied in rodents, rabbits, and dogs. Metoclopramide was well absorbed from the gastrointestinal (GI) tract following oral administration in mice, rats, dogs, rabbits and humans. The percent of oral dose recovered from urine in rats and dogs was 80% and 73% at 24 hours post-dose, respectively. The plasma half-life of orally or parenterally administered drug varied from one to three hours. Metoclopramide was bound to non-dialyzable constituents of the plasma to an extent of 13-22%. Metoclopramide was distributed to most tissues but concentrated particularly in the kidneys, liver, heart, adrenal, and thymus. In mice and rats, metoclopramide was distributed to the brain following either oral or parenteral administration. Tissue levels were comparatively low at 24 hours post-dose. In rats, dogs, and rabbits, metoclopramide was partially metabolized to five or six different metabolites. The most common metabolites in the rat and dog were N-monodeethylated form and a hippuric acid derivative. In rats and dogs, a significant portion of the administered dose was eliminated in the urine as unchanged drug (30-40% of urinary content). Urinary excretion was the major route of elimination, accounting for about 73% of an oral dose in dogs and about 82% of an oral dose in rats. All of the drug was

excreted by 24 hours. Biliary excretion accounted for approximately 2% of the total dose.

Metoclopramide toxicity has been adequately characterized in toxicology studies conducted by the innovator (NDA 17,854 and NDA 21,793). The sponsor did not conduct any nonclinical studies. In repeat-dose toxicology studies in rats, the target organs of toxicity appeared to be the mammary glands (increased secretion and increased development of ducts and acinar tissue) and liver (elevation of liver enzymes). In dogs, the CNS (decreased activity, vocalization, chewing, tremors and hypothermia) appeared to be the target organ. As recommended, the sponsor conducted a search of four large databases (Medline, Derwent Drug Files, Biosis and Embase) from 1997 to 2007. No new information was identified in any publication that would significantly impact the labeling of Metozolv.

Metoclopramide was negative in the Ames test, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat and human hepatocytes, and the *in vivo* rat micronucleus assay. However, metoclopramide was positive in the *in vitro* Chinese hamster lung cell /HGPRT forward mutation assay and the *in vitro* human lymphocyte chromosome aberration assay. The sponsor presented (on page 307 of the NDA) a published report from the European Environmental Mutagen Society [Copenhagen, Denmark, 1999 by Lafouge P et al. (Metoclopramide: Absence of genotoxic potential following the basic ICH battery of tests. *Pharmacol Toxicol* 1999;85 (Suppl. 1):56] that described evaluation of genotoxicity using the Ames test, mouse lymphoma assay, and mouse micronucleus test. In this report, metoclopramide was found to be negative in the Ames test, mouse lymphoma assay, and mouse micronucleus test.

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.

Metoclopramide was not teratogenic 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. The sponsor presented findings from a recently published

study in mice that indicated that metoclopramide-induced hyperprolactinemia may have suppressive effects on ovarian function and may have a negative impact on mouse embryo implantation (Panzan MQ et al. Metoclopramide-induced hyperprolactinaemia caused marked decline in pinopodes and pregnancy rates in mice. *Hum Reprod.* 2006;21: 2514-20).

Conclusions: From a nonclinical standpoint, this NDA is recommended for approval for the proposed use.

Unresolved toxicology issues: None

Recommendations: From a nonclinical standpoint, this NDA should be approved.

Suggested labeling: The sponsor should be asked to modify the proposed label of Metozolv as suggested in the "Executive Summary: Recommendations on Labeling".

Signatures:

Reviewer Signature _____
Tamal K. Chakraborti, Ph.D.
Pharmacologist
Division of Gastroenterology Products

Acting Team Leader Signature _____ Concurrence Yes ___ No ___
David B. Joseph, Ph.D.
Acting Pharmacology Team Leader
Division of Gastroenterology Products

cc:
Original NDA
DGP
DGP/RPM/MDewey
DGP/TChakraborti
DGP/DJoseph

RD/Init.: D. Joseph 9/12/08, 9/25/08

APPENDIX/ATTACHMENTS

None

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tamal Chakraborti
9/25/2008 01:28:31 PM
PHARMACOLOGIST

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10/1/2008 04:49:12 PM
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