CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-574

Pharmacology Review(s)

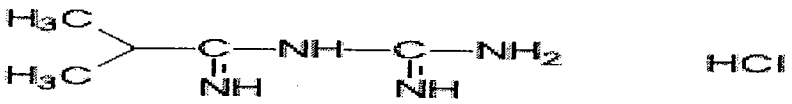
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-574.
Review number:1
Sequence number/date/type of submission: 000/December 17, 2002/Original NDA application [505(b) 2].
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Andrx Labs, Inc. 401 Hackensack Avenue, 9th Floor, Hackensack, NJ 07601.
Manufacturer for drug substance: Andrx Pharmaceutical, Inc. 4955 Orange Drive, Ft. Lauderdale, FL 33314.

Reviewer name: Shen Xiao
Division name: Division of Metabolic and Endocrine Drug Products.
HFD #: 510
Review completion date:

Drug:

Trade name: Fortamet
Generic name (list alphabetically): Metformin Extended-release tablets
Code name: N/A
Chemical name: Metformin Hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride).
CAS registry number:[1115-70-4]
Mole file number: N/A
Molecular formula/molecular weight: $C_4H_{11}N_5.HCl/165.63$
Structure:



Relevant INDs/NDAs/DMFs: IND 55962 (Fortamet)/NDA 20357 (Glucophage)/NDA 21202(Glucophage)

Drug class: Antihyperglycemic agent

Indication: Type 2 diabetic mellitus

Clinical formulation: A white to off-white round, standard concave tablet with one hole on each side. It contains 500 or 1000 mg metformin HCl, BP and consists of an immediate-release core tablet and a porous membrane. The core is the active drug substance, surfactant and binder. Excipients are all commonly used pharmaceutical ingredients. Most are USP/NF compendia grade. The unit dose compositions of Metformin HCl extended-release tablet are described in the following table. The level of the inactive ingredient povidone ([ ] mg/tablet/day) appears to be greater than the maximum concentration for the same route administration in a currently marketed drug product. However, based on the toxicity studies in both rats and dogs, the doses of

Povidone K-90 in the range of 325 to 3,240 mg/day should be safe (B.V. Robinson, et al. 1990. PVP-A Critical Review of the Toxicology of Povidone). All other excipients have been used in currently marketed drug products and are below the maximum approved concentration for the same route of administration.

Composition of Metformin HCl Extended-release (XT) Tablets, 500mg and 1000mg

	Formulation of Metformin E-R tablets			
	500mg		1000mg	
Components	% w/w	mg/tablet	% w/w	mg/tablet
CORE				
Metformin Hydrochloride, BP		500		1000
Sodium Lauryl Sulfate, NF				
Povidone K-90 USP				
Magnesium Stearate, NF				
Coating				
Cellulose Acetate NF				
Triacetin, USP				
Polyethylene Glycol 400, NF				
Candelilla Wax				
	-	-	-	-
	-	-	-	-
	-	-	-	-
	-	-	-	-
Total	100	631.67	100	1225.69

Route of administration: Oral

Proposed use: An extended-release formulation of metformin hydrochloride designed for once-a-day oral administration [ ]

Disclaimer: Some material may be taken directly from sponsor's submission.

PHARMACOLOGY/TOXICOLOGY REVIEW

Introduction and Drug History: Metformin (N, N-dimethylimidodicarbonimidic diamide) is a member of the biguanide class of oral antihyperglycemics. It has been used worldwide for over 30 years. In the United States, it has been commercially available since 1995. Metformin improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Unlike sulfonylureas, it generally does not produce hypoglycemia in either

patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. The pharmacological mechanisms of metformin include the decrease of hepatic glucose production, decrease of intestinal glucose absorption and increase of insulin sensitivity by enhancing peripheral glucose uptake and utilization. Clinical application of this drug is to lower blood glucose in patients with NIDDM whose hyperglycemia can not be satisfactorily managed on diet and exercise alone and use concomitantly with a sulfonylurea or insulin when diet, exercise, or a sulfonylurea or insulin alone does not result in adequate glycemic control.

Metformin hydrochloride is currently marketed in the United States as Glucophage. Two types of clinical formulations, the immediate-release Glucophage (500mg, 850mg, and 1000mg tablets) and extended release metformin hydrochloride products-Glucophage XR (500mg tablet) are approved. It is recommended that the immediate-release Glucophage be administered in divided doses, twice or three times daily with the total maximum daily dose not to exceed 2550mg. For Glucophage XR, the maximum recommended daily dose in adult is 2000mg. This new NDA, Fortamet (Metformin XT), was developed as an extended-release formulation of metformin hydrochloride to provide a same effect on glycemic control compared to the immediate-release formulation but with once daily dosing. The reduced frequency of administration will be more convenient for patients, which may lead to improved patient compliance. Compared to Glucophage XR, it provided safety and efficacy data at dose of 2500mg and has both 500mg and 1000mg tablets available. A 500mg tablet of Fortamet is physically significantly smaller than the same dosage of Glucophage XR, which can be an advantage for diabetic patients who have difficulty swallowing due to the diabetic peripheral neuropathy complication.

A comprehensive battery of pre-clinical pharmacology and toxicology studies for the metformin immediate release tablet has already been performed (Glucophage, NDA 20-357). The overall Cmax levels of Fortamet are expected to be lower than with Glucophage (however, AUC may actually increase). The extended gastrointestinal exposure with this new formulation could result in GI toxicity that has not been characterized with Glucophage. To study the potential gastrointestinal effect of this extended release formulation, a three-month oral gastrointestinal toxicity study in beagle dogs with Fortamet was conducted (IND 55962). This study compared the gastrointestinal toxicity and PK data between this extended release formulation and the approved Glucophage immediate-release formulation.

Studies reviewed within this submission: As indicated earlier, a three-month oral gastrointestinal toxicity study in dogs was provided. No other additional animal studies are considered necessary.

Study title: A three-month oral gastrointestinal toxicity study in Beagle dog:

Key study findings: Fortamet (metformin XT) does not enhance the gastrointestinal toxicity of metformin produced by an immediate-release formulation.

Study no:TX-155-01
Volume #, and page #: Volume 21-22/ Pages 63-686
Conducting laboratory and location: [redacted]

Date of study initiation: 07/28/99
GLP compliance: y
QA report: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Metformin XT, lot# P99148; Glucophage, lot# 9F07704; Metformin XT Placebo Tablet, Lot# P99105
Formulation/vehicle: 500mg/tablet for both Metformin XT and Glucophage. The formulation of Metformin XT is showed in the form of page 2. Placebo is the same formulation without Metformin and does not have a shell-like structure.
Methods: The study group design and dosage levels tested were as follow:

Group	No. of Animals		Dosage of Material	Dosage Level (mg/dog/day)
	Males	Females		
1	8	8	Placebo tablets	0
2	8	8	Metformin XT tablets	500
3	8	8	Glucophage tablets	500

Dosing:

Species/strain: Beagle dogs
#/sex/group: 8/sex/group
Age: 5-6 months
Weight: 6.5-11.4kg for male dogs and 6.4 to 10.4 kg for female dogs
Doses in administered units: 500mg/tablet /day (50mg/kg in a 10 kg dog). Females in general received a higher metformin dose, on a mg/kg basis, than males due to their small size.
Route: Oral
Dose selection: The dose selection was based on the description of 78-week toxicology study in dogs with Glucophage. In that study, the minimal toxic dose was 50mg/kg, which was approximately equivalent to the maximum recommended clinical dose of 2550mg. Higher doses produced 50-100% mortality with clinical signs of gastrointestinal distress and vascular lesions and degenerative changes in the brain, heart, kidney and skeletal muscle.

Observations and times:

Clinical signs: General health/mortality checks were performed twice daily. Detailed clinical observations were performed weekly during the study and on the day of scheduled euthanasia.

Body weights: Twice prior to the initiation of treatment (day –40 or –26 and day –1) and then recorded weekly. All animals were fasted prior the day 92 body weight measurements.

Food consumption: Measured daily from day –6 to day -1 and then from day 1 to the day prior to scheduled euthanasia. Summarized weekly as grams/animal/day

Hematology: N/A
Clinical chemistry: N/A

Gross pathology: All animals were subjected to a complete gross necropsy examination at the time of death or scheduled euthanasia (day 92, 93 or 94). The necropsy examination included evaluation of the external surfaces of the body and all viscera.

Organs weighed: N/A

Histopathology: Any gross lesions of the gastrointestinal tract (including esophagus, stomach, duodenum, jejunum, ileum, cecum and colon) stained with hematoxylin and eosin were examined microscopically.

Toxicokinetics: Blood samples were collected from each dog in groups 2 and 3 prior to dosing and at approximately 2,4,8,12 and 24 hours following dosing on day 1 and day 85, and at approximately 48 hours following dosing on day 85.

Other: Statistical analysis was using ANOVA and all tests were two-tailed with minimum significance level of 5%. Histopathological data were analyzed using Fisher's Exact Test with one-and two-tailed probability.

Results:

Mortality: One female on metfomin XT and three females on Glucophage died on days 45, 33, 57 and 85, respectively during the study.

Clinical signs: The incidence of post-dose vomitus, mucoid material in the cage/tray, soft stools and salivation in both male and females treated with Glucophage was higher than the metformin XT and placebo groups. For males in the Glucophage group, there was an increase in the incidence of post-dose diarrhea compared to the metformin XT and the placebo groups. The overall incidence of clinical signs of gastrointestinal toxicity were decreased in the metformin XT group compared to the Glucophage group with the exception of post-dose mucoid stools in the male, which occurred at the same frequency in both groups.

Body weights: No statistically differences in mean body weights during the study.

Food consumption: The males in the metformin XT and Glucophage groups had significantly decreased food consumption during days 1 to 8. Males in the Glucophage group also had significantly decreased food consumption during the last week of the study (days 85 to 92). Food consumption was significantly decreased during most of the study for females in the Glucophage group and only days 29 to 36 in the metformin XT group. Data were summarized in the following tables.

Summary of Food Consumption in Male Dogs

Day	Group 1	Group 2	Group 3
	Placebo	Metformin XT 500mg	Glucophage 500mg
	Mean±SD	Mean±SD	Mean±SD
1-8	347.8±31.49	322.1±50.67*	322.3±47.91*
8-15	337.6±23.93	323.6±41.79	331.4±35.66
15-22	325.0±21.15	315.1±42.24	322.6±25.06
22-29	324.0±30.58	320.5±34.83	319.0±29.09
29-36	316.8±40.81	314.9±46.12	312.2±48.17
36-43	328.9±31.93	323.7±37.97	326.1±42.7
43-50	350.2±27.52	346.4±34.07	348.2±31.41
50-57	329.7±21.11	329.0±23.5	324.3±25.49
57-64	317.6±50.37	323.5±46.89	320.3±51.48
64-71	313.7±25.11	313.0±25.94	309.1±28.26

71-78	310.5±26.35	313.5±19.57	312.0±23.40
78-85	324.8±22.90	326.2±25.26	318.8±37.03
85-92	320.2±14.69	317.7±19.19	300.5±56.78*

*: P<0.05 compared to control (group1, placebo)

Summary of Food Consumption in Female Dogs

Day	Group 1	Group 2	Group 3
	Placebo	Metformin XT 500mg	Glucophage 500mg
	Mean±SD	Mean±SD	Mean±SD
1-8	311.5±60.47	300.2±67.13	271.6±75.10**
8-15	314.9±48.69	310.1±49.99	290.5±70.84
15-22	299.2±48.68	301.4±46.73	277.3±52.44
22-29	302.1±40.60	290.1±64.33	255.0±61.80#
29-36	307.4±51.34	273.8±80.12*	254.9±65.65#
36-43	309.2±48.83	292.0±64.21	271.6±61.44**
43-50	321.6±51.39	302.6±65.95	241.3±111.01#
50-57	315.4±39.27	303.3±57.43	270.9±84.48**
57-64	307.5±52.45	288.9±59.32	267.9±86.00*
64-71	301.7±44.57	283.6±63.81	249.0±69.03#
71-78	290.6±41.21	282.6±55.97	263.9±78.70
78-85	302.8±55.37	304.6±55.41	265.8±97.25*
85-92	285.4±55.38	288.8±60.38	276.8±64.05

*: P<0.05; **: P<0.01; #: P<0.001 compared to control (group1, placebo).

Gross pathology: There were no remarkable gross necropsy findings in the animals that survived. Data were summarized in the following tables:

Necropsy Findings in Male Dogs (Scheduled Euthanasis- Days 92-94).

Necropsy findings	Group 1 Placebo	Group 2 Metformin XT 500mg	Group 3 Glucophage 500mg
Number of animals examined	8	8	8
All tissues within normal limits	6	5	7
Heart -Hematocyst(s)	0	1	0
Liver -Misshapen -cyst	0 1	0 0	1 0
Lung -discoloration	0	1	0
Skin -scabbing	1	0	0
General comment -Final clinical observation not apparent postmortem	0	1	0

Necropsy Findings in Female Dogs (Scheduled Euthanasis- Days 92-94).

Necropsy findings	Group 1 Placebo	Group 2 Metformin XT 500mg	Group 3 Glucophage 500mg
Number of animals examined	8	7	5
All tissues within Normal limit	4	3	4
Gallbladder -foci	0	0	1
Heart -hematocyst (s)	0	1	0
Pituitary gland -cyst	2	1	0
Skin -scabbing -open lesion	1 1	2 1	1 0
Thymus -small	1	0	0
Whole body/carcass -body fat depletion	1	0	0
General comment -reproductive tissues swollen -final clinical observation not apparent postmortem	1 0	0 2	0 0

Gross necropsy findings for the one dead female dog treated with metformin XT included reddened mucosa of the colon and stomach, reddened pancreas and thyroid, dark red thymus and a focus on the proximal pulmonary trunk of the heart. Necropsy findings for 3 dead female dogs treated with Glucophage included foci in cecum and rectum, foci on the ventricles of the heart; abnormal contents in the oral cavity, small intestine, large intestine, and pericardium; reddened mucosa of the stomach, duodenum, jejunum, ileum and rectum; reddened pancreas, thyroid and mandibular lymph nodes; dark red and enlarged pancreatic lymph nodes, dark red mediastinal and mesenteric lymph nodes, dark red thymus, cortical-medullary juncture of the kidney, fluid contents in the thoracic cavity, and mottled lungs.

Histopathology: No test article-related lesions were observed microscopically in any of the organs examined from animals euthanized at study termination. The incidence of histopathological findings was comparable between the control and the test article-treated groups. All lesions observed were considered agonal or spontaneous. No lesions were observed in any of these dogs which were of a severity which would have caused death.

Toxicokinetics: In the metformin group, the female dog that died on day 45 had the highest plasma exposure, in terms of AUC in the group on day 1. In the Glucophage group, the plasma drug exposure, in terms of AUC on Day 1 for the three female dogs that died were among the five highest values. The mean values of toxicokinetic parameters on days 1 and 85 are summarized in the following tables.

The Toxicokinetic Parameters of Metformin XT and Glucophage in Dogs on Day 1 and Day 85.

Treatment	Cmax (ng/ml)	Tmax (hr)	T lag* (hr)	AUC_{0-24} (ng.hr/ml)	$T_{1/2}$ (hr)
Metformin XT					
Day 1					
Males	3009±986	3±1	0	20657±7782	5.1
Females	5781±2269	4±2	0	42418±11644	4.4
Day 85					
Males	4148±1379	3±1	0	30621±10157	5.5
Females	8106±5607	3±1	0	54415±36680	2.2
Glucophage					
Day 1					
Males	11775±5532	2±0	0	45212±14143	5.9
Females	15076±3188	2±0	0	56707±13627	5.6
Day 85					
Males	11530±2332	2±0	0	48677±6863	7.1
Females	29050±14671	2±0	0	95574±29055	6.5

* T lag: Sampling point preceding the one at which plasma concentrations first became quantifiable.

For both metformin XT and Glucophage groups, females received an approximately 11-12% higher mg/kg dose of metformin than males on day 1 and an approximately 14-15% higher mg/kg dose of metformin than males on day 85. In the metformin XT groups, the Cmax and AUC_{0-24h} values in females were approximately 2 times the values of male on both days 1 and 85. In the Glucophage group, the Cmax and AUC_{0-24h} values in females were approximately 1.3 times the values of males on day 1 and approximately 2.0-2.5 times the value of males on day 85.

Exposure to metformin was higher in the Glucophage group than the metformin XT group. No accumulation was noted in males receiving Glucophage. Some accumulation was noted in males and females receiving metformin XT and in females receiving Glucophage.

Summary of individual study findings: One metformin XT-treated female died (on day 45) and three Glucophage-treated females died (on day 33, 57 and 85, respectively) during the study. Signs of gastrointestinal toxicity were observed in these dogs prior to death. Deaths in females were probably due to higher drug exposures in females in these dogs in particular.

Clinical signs of gastrointestinal toxicity were observed in both metformin XT and Glucophage groups with a significantly higher incidence in the Glucophage group. These gastrointestinal clinical signs commonly occurred during daily post-dose included vomitus, mucoid material in the cage/tray, mucoid stools, and soft stools. An increased incidence of salivation was noted in males and females in the Glucophage group.

There were no treatment-related changes in body weight. The decreased food consumption was noted in males treated with metformin XT and Glucophage during days 1-8 and in females treated with Glucophage during most of the study period.

Necropsy findings related to gastrointestinal toxicity were generally limited to animals that died and included reddened mucosa of the stomach, duodenum, jejunum, ileum, colon, and rectum; foci in the cecum and rectum; and abnormal contents in the oral cavity and small and large intestine. No remarkable necropsy findings were noted at study termination. No test article-related lesions were observed microscopically in any of the organs collected at scheduled euthanasia. The incidence of histopathological findings was comparable between the control and test article-treated groups.

Toxicology summary: In this three month toxicity study comparing metformin XT and Glucophage, oral administration of metformin XT at a dosage of 500mg/dog/day produced fewer signs of gastrointestinal toxicity compared to oral administration of Glucophage at the same dose level (plasma concentration showed that the exposure to metformin was higher in the Glucophage group than the metformin XT group). There were one drug-related death in metformin XT treated group and three drug-related deaths in Glucophage group. Therefore, the metformin XT does not exhibits more gastrointestinal toxicity than the marketed product, Glucophage.

Toxicology conclusions: Based on this three month dog gastrointestinal toxicity study, the results indicated that the extended-release formulation, metformin XT, does not enhance the gastrointestinal toxicity of metformin produced by an immediate-release formulation.

Overall Summary and Evaluation

Fortamet (Metformin XT), was developed as an extended-release formulation of metformin hydrochloride to provide a same effect on glycemic control compared to the immediate-release formulation with once daily dosing. Metformin hydrochloride is currently marketed in the United States as Glucophage. It included two types of clinical formulations, the immediate-release Glucophage and extended release metformin hydrochloride products-Glucophage XR (500mg tablet). Compared to Glucophage XR, Fortamet has both 500mg and 1000mg tablets available and its tablet is physically significantly smaller than the same dosage of Glucophage XR, which can be an advantage for diabetic patients who have difficulty swallowing due to the diabetic peripheral neuropathy complication.

The proposed metformin XT formulation consists of an immediate-release core tablet and a porous membrane. The drug diffuses through laser-drilled holes in the membrane by osmotic pressure. The porous membrane itself is designed to remain largely intact after passing through the gastrointestinal tract and is, therefore, eliminated in the feces.

Safety Evaluation: Metformin has become an established treatment for type II diabetes since its introduction in 1957. Metformin hydrochloride was first approved in the United States in 1994. A comprehensive battery of pharmacology and toxicology studies has been conducted for the approved Glucophage (NDA 20,357). Since the Fortamet is an extended release formulation, the extended gastrointestinal exposure with this new formulation could result in enhanced GI toxicity compared to the immediate release Glucophage. Therefore, a three month bridging GI toxicity

study in dogs was provided with this NDA application to compare the difference between metformin XT and Glucophage.

In this three-month toxicity study comparing metformin XT and Glucophage, oral administration of metformin XT at a dosage of 500mg/dog/day produced fewer signs of gastrointestinal toxicity compared to oral administration of Glucophage at the same dose level (toxicokinetic parameters showed that the exposure to metformin was higher in the Glucophage group than the metformin XT group). There was one drug-related death in metformin XT treated group and three drug-related deaths in Glucophage group. Therefore, based on this three-month dog gastrointestinal toxicity study, the results indicated that the extended-release formulation, metformin XT, does not enhance the gastrointestinal toxicity of metformin.

In term of the excipients in this formulation, the level of one excipient in the formulation, povidone ([redacted] mg/tablet/day), appears to be greater than the maximum concentration for the same route administration in a currently marketed drug product. However, based on the toxicity studies in both rats and dogs, the doses of Povidone K-90 in the range of 325 to 3,240 mg/day should be safe (B.V. Robinson, et al. 1990. PVP-A Critical Review of the Toxicology of Povidone). All other excipients have been used in the currently marked drug products and below the maximum concentration for the same route of administration. Most are USP/NF compendial-grade.

In conclusion, there has been considerable experience with metformin hydrochloride and toxicities are well characterized. The three-month dog gastrointestinal toxicity study has indicated that the extended-release formulation, metformin XT, does not enhance the gastrointestinal toxicity of metformin. It is not expected that any additional systemic toxicities will be encountered, particularly since the exposure to metformin was higher in the Glucophage than the metformin XT at the same dosage. The sponsor proposed the highest daily dose of metformin XT (2500mg/day) fall within those currently approved for Glucophage (2550mg/day as a maximum for Glucophage). Based on the information contained in the Summary Basis of Approval (SBA) for Glucophage (NDA 20, 357) and the published literature, no additional warnings, precautions, or contra-indications are warranted for the label.

Labeling recommendations: Labeling with this application is identical to the Glucophage (NDA 20, 357) package insert. No revisions of the labeling are needed.

Reviewer signature:

Shen Xiao, Reviewer Pharmacologist Date

Team leader signature [concurrence/non-concurrence]:

Jeri El-Hage, Supervisory Pharmacologist Date

cc: IND Arch
HFD-510
HFD-510/ Jeri El-Hage/Jena Weber /Shen Xiao

FILE NAME: NDA 21,574. REVIEW.DOC

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

/s/

Shen Xiao
6/11/03 12:50:59 PM
PHARMACOLOGIST

Jeri El Hage
6/11/03 01:52:12 PM
PHARMACOLOGIST

NDA Filing Meeting Checklist

NDA #: 21574 DRUG:Fortamet (Metformin HCl)
Sponsor: Andrx Labs, Inc

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	y		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	y		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	y		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? (Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA - e.g., safety pharm, genotox, reprotox, chronic tox, carcinogenicity)	y		Have electronic files of the carcinogenicity studies been submitted for statistical review? A three-month oral gastrointestinal toxicity study in Beagle dogs to bridge between Glucophage XR and Fortamet.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	y		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?			N/A
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	y		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	y		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	y		
10) Reasons for refusal to file:			

Shen Xiao
Reviewing Pharmacologist

Supervisory Pharmacologist

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

/s/

Shen Xiao
2/10/03 05:32:55 PM
PHARMACOLOGIST

Jeri El Hage
2/11/03 02:16:37 PM
PHARMACOLOGIST