CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-589

<u>MEDICAL REVIEW(S)</u>

MEMORANDUM

Date: October 30, 2003
From: Armando Oliva, MD
To: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
Subject: Team Leader Memorandum for NDA 21589, Baclofen ODT

This application is a 505(b)2 application to market a baclofen orally disintegrating tablet (ODT). The proposed indication is the same as the currently approved conventional tablet. The application relies on the demonstration of bioequivalence between the 20mg ODT ("test") and the currently marketed 20mg conventional tablet ("reference"). The sponsor plans to market a 10mg and 20mg ODT. They have requested a biowaiver for the 10mg strength.

Dr. Rosloff provides the pharmacology toxicology review and Dr. Heimann provides the CMC review. Dr. Rosloff finds the application approvable, but recommends that the sponsor complete a complete genotoxicity battery (per ICH guidelines) as a phase IV commitments.

Dr. Bastings provides the clinical review. Dr.Noory provides the review for the Office of Clinical Pharmacology and Biopharmaceutics.

The original baclofen NDA (17-851) was approved in 1977 and is held by Novartis, but they no longer market this product. The reference listed drug is marketed by Watson Labs. Baclofen is indicated for the treatment of spasticity in patients with multiple sclerosis and in some patients with spinal injuries and other spinal cord diseases. The efficacy of baclofen in stroke, cerebral palsy, and Parkinson's Disease has not been established.

The application consists of two pharmacokinetic studies: SP692 and SP741.

Study SP692 was an *in vivo* bioequivalence study in 28 subjects (14M/14F). This was a single dose, open-label, two-treatment single-dose replicate design crossover study. Each subject received 20mg of the test drug or 20mg of the reference drug in a random order, followed by the other formulation after a 7-day washout period. Each tablet was administered with water. This was then replicated in the same subjects. Serial plasma concentrations were obtained for 24 hours following each administration.

A total of 25 subjects completed the study. The pharmacokinetic results are shown in Table 1. The results indicated that the 20mg ODT is bioequivalent to the reference product with respect to C_{max} and AUC. The percent mean ratios of C_{max}, AUC_{0-t} and $AUC_{0 \to \infty}$ were 96% for all three. Dr. Noory concludes that the two products are bioequivalent. The sponsor requests a waiver for the 10mg strength, which Dr. Noory also finds acceptable.

Table 1: Study SP692 – Pharmacokinetic Parameters

Summary of the Pharmacokinetic Parameters of Plasma Baclofen for Treatments A and B

	Plasma Baclofen									
Pharmacokinetic Parameters	Treatment A				Treatment B					
	First Replicate		Second Replicate		First Replicate		Second Replicate			% Mean *
	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI *	Ratio
Cmax (ng/mL)	325.56	78.71	328.01	85.61	334.99	79.73	343.83	66.73		
Tmax (hr)	1.50	0.789	1.33	0.774	1.36	0.515	1.27	0.753		
AUC(0-t) (ng*hr/mL)	1817	390.0	1843	393.5	1889	325.0	1905	355.6		
AUC(0-inf) (ng*hr/mL)	1893	396.4	1919	405.1	1968	340.5	1989	373.3		
T1/2 (hr)	5.66	0.829	5.64	0.761	5.60	0.809	5.74	0.747		
Kel (1/hr)	0.125	0.0185	0.125	0.0174	0.127	0.0194	0.123	0.0173		
AUCR	0.959	0.0170	0.960	0.0142	0.960	0.0161	0.958	0.0150		
ln(Cmax)	5.757	0.2431	5.762	0.2493	5.785	0.2514	5.822	0.1981	92.2- 99.7	95.9
ln(AUC(0-t))	7.482	0.2227	7.496	0.2256	7.530	0.1739	7.535	0.1883	91.8- 99.8	95.7
ln(AUC(0-inf))	7.524	0.2184	7.537	0.2229	7.570	0.1738	7.578	0.1893	91.9- 99.7	95.7

Treatment A = 1 x 20 mg Baclofen ODT Administration (Schwarz Pharma, Inc.): Test
Treatment B = 1 x 20 mg Baclofen IR Tablet Administration (Watson Laboratories, Inc.): Reference
* = Based on LS means from Table 11.

Physical examination, vital signs, ECG, and laboratory data were collected at screening and study completion. There were no new or unexpected safety signals generated from this small PK study. I refer the reader to Dr. Basting's review for more details.

A second study (study SP741) was performed in 18 subjects (17 completers) to evaluate the pharmacokinetics of the 20 mg orally disintegrating tablet when taken without water and compared with the reference listed drug. The two products were bioequivalent in this study as well (table A.2.3 of the OCPB review, page 28, not shown here). The results of this study can be used to support a statement in labeling that the orally disintegrating tablet can be taken without water.

Regarding the safety findings in this study, Dr. Bastings notes the occurrence of petechiae in the buccal mucosa of 2 subjects in this study after taking the ODT. This was not observed in the earlier study when the ODT was taken without water. The petechiae were observed 7 days after taking study medication and resolved spontaneously after a day and half. Dr. Bastings recommends that this adverse event be better characterized post-approval.

There were no efficacy studies performed. This 505(b)2 application relies on the efficacy of baclofen, as established in NDA 17-851. Similarly there are no safety studies as the sponsor relies on the human safety and animal toxicology from the original NDA. At the pre-NDA meeting, we agreed this approach was acceptable, with the exception that the sponsor would need to conduct a genotoxicity battery. We agreed this could be deferred to phase 4.

Dr. Bastings conducted several MedLine searches for reports/publications of post-marketing baclofen toxicities. He found numerous reports suggesting that the currently approved labeling is not up to date with regard to geriatric use, overdose, and in patients with renal failure.

He recommends approval, although recommends

I agree that this should not be a prerequisite for approval, as the currently marketed baclofen tablet uses the essentially the same label. Since the reference product is a subject of an ANDA, I recommend we

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In addition, we should also obtain a phase IV agreements with the sponsor as Dr. Bastings and Dr. Rosloff recommend.

Armando Oliva, M.D.
Neurology Team Leader

MEMORANDUM

Date: October 17, 2003
From: Armando Oliva, MD
To: Russell Katz, MD
            Director, Division of Neuropharmacological Drug Products
Subject: Team Leader Memorandum for NDA 21589, Baclofen ODT

This application is a 505(b)2 application to market a baclofen orally disintegrating tablet (ODT). The proposed indication is the same as the currently approved conventional tablet. The application relies on the demonstration of bioequivalence between the 20mg ODT ("test") and the currently marketed 20mg conventional tablet ("reference"). The sponsor plans to market a 10mg and 20mg ODT. They have requested a biowaiver for the 10mg strength.

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The application consists of two pharmacokinetic studies: SP692 and SP741.

Study SP692 was an *in vivo* bioequivalence study in 28 subjects (14M/14F). This was a single dose, open-label, two-treatment single-dose replicate design crossover study. Each subject received 20mg of the test drug or 20mg of the reference drug in a random order, followed by the other formulation after a 7-day washout period. Each tablet was administered with water. This was then replicated in the same subjects. Serial plasma concentrations were obtained for 24 hours following each administration.

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Armando Oliva, MD, HFD-120
NDA 21589

Team Leader Memorandum
Baclofen ODT

Page 2 of 3
October 17, 2003

Table 1: Study SP692 – Pharmacokinetic Parameters

Summary of the Pharmacokinetic Parameters of Plasma Baclofen for Treatments A and B

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In addition, we should also obtain a phase IV agreements with the sponsor as Dr. Bastings and Dr. Rosloff recommend.

Armando Oliva, M.D.
Neurology Team Leader

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

RESPONSE TO APPROVABLE LETTER

Brand Name:	—
Generic Name:	Baclofen
Sponsor:	Schwartz Pharma
Indication:	Spasticity
NDA Number:	21-589
Original Receipt Date:	12/31/02
Clinical Reviewers:	Eric Bastings, MD
Review Author:	Eric Bastings, MD
Review Completed:	10/16/03

Table of Contents

Clinical Review for NDA 21-589

Executive Summary

I.   Recommendations

A.   Recommendation on Approvability

NDA 21-589 is a 505(b) (2) application for a new dosage form of baclofen (orally disintegrating tablets). The proposed indication is the same as for the approved "conventional" tablet. The safety and efficacy of baclofen 10mg and 20mg tablets have been established in NDA 17-851. The new dosage form is presented as bioequivalent to the reference listed drug (Watson Labs' baclofen tablet 20 mg), and the benefits and risks of this new dosage form are not different from those of the reference listed drug (with the exception of petechiae in the oral mucosa seen after taking baclofen orally disintegrating tablet with no water). On a clinical perspective, I recommend approval.

B.   Recommendation on Phase 4 Studies and/or Risk Management Steps

Two patients (11%) developed petechiae after taking baclofen orally disintegrating tablets with no water. This adverse event should be better characterized in a repeated dose administration study, which I recommend as a phase 4 commitment.

II.   Summary of Clinical Findings

A.   Brief Overview of Clinical Program

NDA 21-589 is for a new dosage form of baclofen, namely, orally disintegrating tablets. The proposed indication (unchanged from the tablet dosage form approved in NDA 17-851) is the treatment of spasticity in patients with multiple sclerosis and in some patients with spinal cord injuries and other spinal cord diseases.

The clinical program is limited to two studies (protocol SP692 and SP741) in 46 subjects, to establish bioequivalence of the new dosage form of baclofen (orally disintegrated tablet) with the marketed reference listed drug (RLD), at the highest dosage form (20mg).

There is a vast clinical experience with baclofen tablets.

B.   Efficacy

There was no new efficacy study in this NDA. Baclofen is approved for the indication of spasticity resulting from multiple sclerosis and in some patients with spinal cord injuries and other spinal cord diseases. Labeling states that baclofen is mostly useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. Baclofen is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders. The efficacy of baclofen in stroke, cerebral palsy, and Parkinson's disease has not been established.

C.   Safety

This NDA provides limited additional information to the vast clinical experience with baclofen, since patients in the two bioequivalence studies received one to two single doses of the new dosage form. A new safety concern emerged from the second bioequivalence study: two patients (11%) developed petechiae after taking baclofen ODT with no water. That adverse event was not reported when baclofen ODT was taken with water. Even though this adverse event was not considered as related to the study drug by the investigator, its occurrence only after administration of baclofen ODT with no water is, in my opinion, suggestive of a possible relationship to the study drug in the absence of another definite etiology.

In NDA 17-851 studies (original NDA for baclofen tablets), the most common adverse reaction was transient drowsiness (10-63%). Other common adverse reactions were dizziness (5-15%), weakness (5-15%), nausea (4-12%), confusion (1-11%), hypotension (0-9%), headache (4-8%), and fatigue (2-4%).

Baclofen has been associated with a withdrawal syndrome, as discussed in the Warnings section of the baclofen tablet package insert. Patients experiencing this withdrawal syndrome may present a rebound increase in spasticity, hallucinations, seizures, confusion, and elevated temperature.

A dose-related increase in incidence of ovarian cysts was seen in preclinical studies of NDA 17-851. A Phase IV open-label study in multiple sclerosis patients treated with baclofen for up to one year showed an incidence of ovarian cysts similar to the background rate.

No additional adverse events, precautions or warnings have been added to the initial package insert since baclofen tablets were approved in 1977.

D.   Dosing

Dosing is the same as for the reference listed drug. Current labeling recommends individual titration, with a start at a low dosage, and gradual increase until optimum effect is achieved (usually between 40-80 mg daily). The following dosage titration schedule is suggested in

labeling: 5 mg t.i.d. for 3 days, 10 mg t.i.d. for 3 days, 15 mg t.i.d. for 3 days, and 20 mg t.i.d. for 3 days. The total daily recommended dose is of 80 mg (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended.

E.   Special Populations

No new study was conducted in special populations in this NDA.

Gender
Current labeling does not address gender issues. No gender differences were observed in the phase III study of the original baclofen NDA (n = 175).

Ethnic/racial
Current labeling does not address race/ethnic differences.

Pediatric
The sponsor is not planning any pediatric study. A pediatric study was requested at the pre-NDA meeting, but the FDA pediatric rule has been suspended in the interim. The reference listed drug labeling states that safety and effectiveness have not been established in pediatric patients below the age of 12.

Pregnancy
Current labeling lists Pregnancy Category C. Baclofen has been shown to increase the incidence of omphaloceles in fetuses of rats given approximately 13 times the maximum dose recommended for human use (MRD). There was also an increased incidence of incomplete ossification in fetuses of rats given approximately 13 times the MRD, and in fetuses of rabbits given approximately 7 times the MRD. There were no adequate and well-controlled studies conducted in pregnant women. Reference listed drug labeling states that baclofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Reference listed drug (RLD) labeling states that it is not known whether this drug is excreted in human milk. Labeling uses the standard language that "because many drugs are excreted in human milk, caution should be exercised when baclofen is administered to a nursing woman".

Geriatric Use
There are no data on the safety and efficacy of baclofen in the elderly in the RLD labeling. Reference listed drug labeling states the generic statement that "in general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy".

Patients with Renal Impairment
There has been no specific study investigating baclofen in patients wit renal impairment in the original NDA or in this 505 (b) (2). Reference listed drug labeling states that "because baclofen is primarily excreted unchanged by the kidneys, it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function".

Hepatic impairment
Baclofen is excreted primarily by the kidney in unchanged form. Therefore, hepatic impairment is not expected to necessitate any dose reduction. Reference listed drug labeling does not address hepatic impairment.

APPEARS THIS WAY
ON ORIGINAL

Clinical Review

I.   Introduction and Background

A.   Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The sponsor, Schwarz Pharma Inc., has developed a new dosage form for baclofen: an orally disintegrating tablet (10 mg and 20 mg). Conventional immediate release Lioresal (baclofen) tablets was approved on November 22, 1977. Baclofen is an analog of GABA, with anti-spasticity properties.

This 505(b) (2) application is based on the premise that the pharmacokinetics of the orally disintegrating tablet formulation establishes therapeutic equivalence to the reference listed drug (generic baclofen tablet from Watson Labs), which is a "conventional" immediate release formulation. The sponsor has initially proposed the trade name '   ―   or '   ―   DMETS originally reviewed the names   ―   and   ―   (Consult # 03-0016, dated March 18, 2003), and did not recommend the use of these names. In response to DMETS' review of   ―   , and   ―   Schwarz Pharma submitted   ―   as an alternate proposed name. DMETS does not recommend the use of the proprietary name '   ―   either, so that the trade name is still undetermined at the time of writing this review.

The proposed administration regimen is the same as for the reference listed drug: up to 80mg total daily dose (20mg q.i.d). The drug is targeted for the adult population.

B.   State of Armamentarium for Indication(s)

Baclofen is one of the main and oldest spasticity drugs available in the United States. In addition to oral administration (tablets), baclofen may also be administered intrathecally using a pump. The pump administration is reserved for the most severe cases, and is not as a first-line therapy. The main alternative to baclofen is tizanidine, a centrally acting a_2-adrenergic agonist that was approved in 1996 in the tablet form, and in 2002 in the capsule form. A second alternative is diazepam (Valium), a benzodiazepine which may induce dependence and cause a withdrawal syndrome in case abrupt withdrawal. Finally, dantrolene, a muscle relaxant, remains available but is more rarely used because of possible severe hepatotoxicity.

For more focal treatment of spasticity, neural transmission blocks using botulinum toxin, local anesthetics or other chemical agents can also be used. Botulinum toxin is being studied off label for the indication of focal spasticity. Maximum dosage limits its applicability in case of spasticity involving multiple muscle groups.

There are also non-pharmacological alternatives, such as muscle stretching, range of motion exercises, and other physical therapy regimens. Finally, surgery for tendon release or posterior rhizotomy can be applied in selected cases.

C.   Important Milestones in Product Development

The sponsor submitted IND 63,882 for baclofen disintegrating tablet in 2002. The division met with the sponsor in June 2002 to discuss the suitability of existing preclinical and clinical data to support a 505(b) (2) application (pre-NDA meeting). At that time, the sponsor proposed that although the existing preclinical studies may not have been conducted according to current ICH standards, the intent and aims of the current guidelines have been met. The division concurred.

The sponsor proposed to conduct a bioavailability study comparing the new dosage form to Watson Labs' baclofen tablet 20 mg (the reference listed drug) to support the filing of a 505(b) (2) application, and to file a biowaiver for the lower 10 mg strength. The division informed the sponsor that the biowaiver for the 10mg strength was a review issue, based on the results of the bioequivalence study and on the dissolution data. The clinical pharmacology reviewer also requested a food effect study, a study to assess the co administration with or without water, or a suitable justification for not conducting these studies.

Since the application seeks the same indications, strengths, and dosing as the reference listed drug, the sponsor proposed that no further clinical studies are required to support approval of the 505(b) (2) application. The division concurred. The sponsor requested a waiver of pediatric studies.

Chemistry issues were also discussed and agreed upon before the NDA submission. The chemistry reviewer requested stability studies for the drug product according to FDA and ICH guidances, and requested that all potential degradation products be monitored.

The sponsor sent a list of additional questions in September 2002. The sponsor obtained concurrence that the clinical summary as contained in the information package submitted to the Agency is sufficient to support the 505(b)(2), since the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs.

The sponsor reached agreement concerning the format of the application. The division agreed that the sponsor refer to the ISS and ISE from the Lioresal application.

The original NDA contained the study report of protocol SP692, a bioequivalence study of baclofen 20 mg Orally Disintegrating Tablet (ODT), compared to marketed immediate release 20 mg baclofen tablet formulation (reference), manufactured by Watson Laboratories, Inc. This first study was conducted in the fasted state.

The sponsor sent in an August 25, 2003 amendment the study report for a second bioequivalence study of baclofen ODT given without water, compared to marketed immediate release baclofen 20 mg tablet formulation (protocol SP741).

D.   Other Relevant Information

Conventional immediate release Lioresal (baclofen) tablet was approved on November 22, 1977. Lioresal tablets were recently withdrawn by Novartis, and baclofen tablets, owned by Watson Labs, have been designated as the new reference listed drug (RLD). Baclofen has been marketed in several other countries. The sponsor is unaware of a withdrawal of baclofen tablets from any market. Baclofen disintegrating tablets has not been marketed anywhere.

E.   Important Issues with Pharmacologically Related Agents

Baclofen has been associated with a withdrawal syndrome, as is discussed in the Warnings section of the package insert. Patients have experienced a rebound increase in spasticity, hallucinations, seizures, confusion, and elevated temperature. FDA recently added a Boxed Warning and strengthened the Warnings section of the prescribing information of Lioresal Intrathecal (baclofen intrathecal), indicated for use in the management of severe spasticity of cerebral and spinal origin. The warning informs healthcare professionals about rare cases of intrathecal baclofen withdrawal that can lead to life threatening sequelae and/or death in patients who abruptly discontinue therapy.

II.   Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The sponsor is relying on cross-reference to baclofen (Lioresal) NDA 17-851 for preclinical data. In addition, the sponsor has proposed to conduct a complete genotoxicity battery as a phase IV commitment. The division concurred with that approach in the June 2002 pre-NDA meeting. I refer the reader to the FDA chemistry review document for further details.

A. Chemistry

Drug Substance
Generic Name: *baclofen*
Chemical Name: *4-amino-3-(4-chlorophenyl)-butanoic acid*
Molecular Weight: *213.66*

Figure 1: Chemical Structure

$H_2NCH_2CHCH_2COOH$
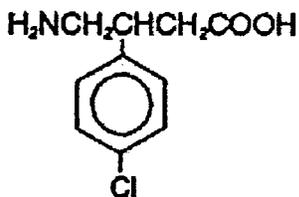
Drug Product
Orally disintegrating tablets will be available as 10 mg or 20 mg tablets. Each tablet contains as inactive ingredients aspartame, microcrystalline cellulose NF, colloidal silicon dioxide NF, crospovidone NE, _ ‗ , magnesium stearate NE, mannitol USP, flavor, and povidone USP.

The sponsor submitted __ accelerated stability data, and is proposing ⟶ expiration dating.

B. Animal pharmacology and toxicology

This section summarizes baclofen preclinical data as presented by the sponsor. I refer the reader to the FDA pharmacology/toxicology review document for further details.

Baclofen is a $GABA_B$ receptor agonist that acts centrally to relax skeletal muscles by suppressing the release of glutamate and aspartate from nerve terminals. This binding is highly stereospecific, with the R-enantiomer having a greater affinity for the ? receptor than the S-enantiomer and neither is active at the $GABA_A$ site. Baclofen is not converted to $GABA_A$ in vivo and baclofen does not alter GABA levels in the rat brain, indicating that the central actions of the drug are mediated by a different mechanism.

Preclinical pharmacology studies in mice, cats, rabbits and dogs showed that baclofen blocks mono- and poly-synaptic spinal reflexes, and also blocks decerebrate rigidity. Baclofen in various animal models showed muscle relaxing activity at doses of 5-10 mg/kg p.o. and 1-3 mg/kg iv. The exact mechanism for its activity is not fully known. Safety pharmacology studies also indicated that baclofen may produce CNS depression (sedation and/or somnolence), ataxia, bradypnea and hypotension.

The pharmacokinetic profile of baclofen is similar between the rat, dog and human. Baclofen is rapidly absorbed and eliminated in animals, primarily through urinary excretion of unchanged drug (similar to humans). Distribution of radioactivity primarily follows the blood flow pattern, with the highest concentrations in the excretory organs. Disposition of drug in the brain showed a slower elimination than that in blood or other tissues. There was limited evidence of enzyme induction but no evidence that repeated doses of baclofen induces its own metabolism. Baclofen does cross the placenta and tissue distribution in the fetus is similar to that reported for the dam. Baclofen was detected in animal milk.

The general toxicity profile included subacute, subchronic, and chronic toxicity studies for up to 1 year in rats at 500 mg/kg/day (380 times the maximum recommended human dose (MRD)) and in dogs at 12 mg/kg/day (approximately 9 X the MRD). Dose limiting toxicity in the dog was related to emesis, and sedation. There was no identified target organ of toxicity. The distribution studies suggested that the liver and kidney may be at higher risk, but clinical parameters, and macroscopic and microscopic findings did not indicate this to be the case. In the rat, there was an increase in urinary incontinence, ascribed to a pharmacological action of the drug. In rats and

dogs, inconsistent transient changes in ALT were noted, but liver microscopic examinations were unremarkable.

A dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands were observed in female rats treated chronically (1-2 years) with baclofen (100-500 mg/kg/day). Baclofen given on an acute or subacute basis has been reported to cause a 30-40% depletion of adrenal epinephrine. As this was mainly a $GABA_A$ response, these pharmacology studies indicate that high-doses of baclofen can affect both receptor subtypes.

Baclofen was not carcinogenic in a 2-year rodent bioassay at maximum tolerated doses of up to 500 mg/kg/day (approximately 380 X MRD).

Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given 20 mg/kg/day (approximately 15 X MRD) at a dose which caused significant reductions in maternal food intake and weight gain. This abnormality was not seen in other developmental studies with mice or rabbits.

There was also an increased incidence of incomplete ossification in fetuses of rats given 20 mg/kg/day (approximately 15 X MRD). An increased incidence of unossified phalangeal nuclei of forelimbs and hind limbs in fetuses of rabbits given approximately 7 X MRD is cited in the product prescribing information. In mice, no teratogenic effects were observed, although reductions in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 and 34 times the MRD.

III.   Human Pharmacokinetics and Pharmacodynamics

A.   Pharmacokinetics

As noted in previous sections, much of the information in this application is based on the published Summary Basis for Approval (SBA) for the conventional immediate-release baclofen tablets, originally approved in 1977 as NDA 17-851 (Ciba-Geigy's Lioresal Tablets). Through the SBA for Lioresal and published literature, it is known that baclofen is rapidly and extensively absorbed and eliminated. According to the published package insert for "conventional" baclofen tablets, absorption may be dose-dependent, being reduced with increasing doses. Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large intersubject variation in absorption and/or elimination. The elimination half-life is approximately 5 1/2 hours.

The sponsor conducted a fasting bioequivalence study comparing immediate release baclofen tablets to the proposed dosage form, orally disintegrating tablets (**Protocol SP 692**). The sponsor reports that the test product had a similar relative rate and extent of availability when compared to the reference product. The sponsor submitted a biowaiver for the lower strength tablet (10mg). The 10mg and 20mg tablets are proportionally similar in active and inactive ingredients and dissolution testing has been conducted. The sponsor later submitted **Protocol SP741**, to evaluate

bioequivalence when baclofen ODT is given with no water. I refer the reader to FDA biopharmaceutics review for a critical analysis of pharmacokinetic data.

Protocol SP 692

Protocol SP 692 was a single-dose, randomized, open-label, 2-treatment, 4-period crossover study to compare the bioavailability of baclofen ODT taken with water to marketed immediate-release 20 mg baclofen tablet (reference), manufactured by Watson Laboratories, Inc.

A total of 28 subjects were enrolled, and 25 subjects completed the study. On each study period (2 periods per drug), patients received a single dose of baclofen 20mg orally disintegrating tablet, or a baclofen 20 mg tablet. There was a 7-day washout interval between each administration.

Baclofen pharmacokinetics were assessed by measuring serial plasma concentrations for 24 hours after administration. The usual bioequivalence criteria (90% confidence interval of the ratio of product means between 80 and 125%) were met. The 90% confidence interval for ln-transformed, AUC_{0-t} and AUC_{0-inf} were respectively 92.2-99.7%, 91.8-99.8%, and 91.9-99.7%.

Protocol SP741

Protocol SP741 was a single-dose, randomized, open-label, two-period crossover study to compare baclofen ODT taken with no water to baclofen tablets (reference). Eighteen healthy subjects were administered a baclofen 20 mg ODT without water or baclofen 20 mg tablet (crossover), separated by a one week washout period. Seventeen patients completed the study. Baclofen ODT given without water had a similar rate and extent of absorption compared to the reference tablet, meeting the requirements for bioequivalence.

B.   Pharmacodynamics

No new pharmacodynamic study was conducted.

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IV. Description of Clinical Data and Sources

A. Overall Data

No new clinical study was conducted, with the exception of the bioequivalence study described in the pharmacokinetics section above. The sponsor refers to baclofen summary basis for approval to support efficacy.

B. Tables Listing the Clinical Trials

Protocol SP 692 and **Protocol SP741** are the only clinical trials.

C. Postmarketing Experience

This drug is a new formulation for an existing product marketed as a generic by several sponsors. The product has been marketed for over 25 years in the United States. No additional adverse events, precautions or warnings have been added to the initial package insert since baclofen tablets were approved in 1977. Baclofen has been associated with a withdrawal syndrome discussed in the Warnings section of the package insert since approval.

D. Literature Review

The sponsor conducted a literature review for the time period after approval (1977-2002). I also conducted a literature Medline search on baclofen (specifics are described in relevant sections).

V. Clinical Review Methods

A. How the Review was Conducted/ Overview of Materials Consulted in Review

The sponsor submitted a copy of the summary basis for approval for NDA 17-851, and a summary of a literature search he conducted. I conducted myself a literature search for new information on baclofen safety/efficacy (specifics are described in relevant sections).

B. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI inspection was requested for ⎯
M.D., Ph. D. is the principal investigator. Results are pending at the time of writing this review.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

Clinical studies were conducted in accordance with accepted ethical standards.

D. Evaluation of Financial Disclosure

The sponsor states that there was nothing to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The efficacy for this new dosage form of baclofen is supported by cross-reference to the reference listed drug. No new efficacy study was conducted.

B. General Approach to Review of the Efficacy of the Drug

I reviewed the summary basis for approval describing the studies supporting baclofen efficacy. I also briefly reviewed the supporting studies published in the literature.

C. Detailed Review of Trials by Indication

Baclofen studies forming the Agency's basis of approval for baclofen tablets

This section reviews the clinical information obtained from baclofen NDA 17-851 summary basis of approval, as presented by the sponsor. I also examined volume 1.1 of NDA 17-851 to verify the sponsor's presentation.

Dose-Ranging Studies
Nine open-label dose-ranging studies in a total of 43 patients were conducted under two different protocols. One protocol studied hospitalized patients and the other studied outpatients with multiple sclerosis or spinal cord disease characterized by spasticity of the skeletal musculature. Data were pooled. Patient ages ranged from 9 to 64 years, but only one patient (age 9) was under age 20. Each patient received baclofen for four weeks. Using a physician global and patient global assessment of spasticity, 85% of patients improved. Muscle tone improved in 50% of patients. Functional status was unchanged. Baclofen optimal dose ranged 40-80 mg daily. Side effects were usually mild and included drowsiness, dizziness, weakness, and nausea. No clinically significant changes in laboratory tests were found.

Phase II Studies
Data from eight Phase II studies conducted in 94 patients (under five different protocols) were pooled. Six studies were double-blind, placebo-controlled, and crossover; two studies were controlled with diazepam. Patient ages ranged 22 to 65, and treatment duration was 4-5 weeks after a one week placebo washout and with a one-week drug-free period between treatment periods. Doses of baclofen started at 5 mg t.i.d. and were titrated up to a maximum 80 mg daily. Fifty-five patients had multiple sclerosis and 39 had other spinal cord disease. The only measurements that could be pooled were patient and physician global evaluations of improvement in the use of spastic limbs and general well-being. The difference in response was statistically significant with regard to global improvement in number of spasms, spastic limb pain, use of spastic limbs, spasticity and general well-being over the treatment period.

Phase III Study
One pivotal study (known as "Protocol 19") was conducted. It was a double-blind, parallel group, placebo-controlled study to evaluate the therapeutic efficacy, safety, and tolerability of baclofen in patients with chronic spasticity due to multiple sclerosis, spinal cord injuries or disease, cerebrovascular disease, or encephalomyelitis. Two hundred seventy-eight patients were enrolled in the study with 175 patients evaluable for efficacy. Patient demographics are described in Table 1.

Table 1: Demographics

Cause of Spasticity	Baclofen n=82	Placebo n =93
Multiple sclerosis	54	52
Spinal cord injury	7	7
Spinal cord disease	13	24
Stroke	6	7
Encephalomyelitis	2	2

Patients were randomly assigned to baclofen or placebo. Table 2 describes the titration schedule.

Table 2: Baclofen dosage

	Outpatients	Inpatients
Week 1	5mg t.i.d. x 3 days 10mg t.i.d. x 4 days	10mg t.i.d. x 3 days 15mg t.i.d. x 4 days
Week 2	15mg t.i.d. x 3 days 20mg t.i.d. x 4 days	20mg t.i.d.
Week 3-5	10mg to 20mg additional if needed, not to exceed 80mg daily	10mg to 20mg additional if needed, not to exceed 80 mg daily

Table 3 shows the optimal doses achieved in the baclofen group. It is unclear if the category "none" in table 3 means that no optimal dose was reported or that an optimal dose was not achieved.

Table 3: Optimal baclofen dose achieved

	20 mg/d	40 mg/d	60 mg/d	70 mg/d	80 mg/d	None	Unknown
No. of Patients	1	3	10	0	25	42	1

Duration of treatment was five weeks for each treatment, with clinical evaluations at baseline, three weeks, and five weeks. Table 4 lists the clinical parameters that were assessed and the method of rating response to the study treatment. There was no well defined primary outcome.

Table 4: Clinical parameters measured in Protocol 19

Mood
> 4 point scale of depression, euphoria, irritability

Pain and frequency of flexor spasms
> 4 point scale of frequency 1 = 1-10/d
>   2 = 11-50/d
>   3 = 51-100/d
>   4 = >100/d

Degree of tendon stretch reflexes of the knees
> 5 point scale ⇒ absent, diminished, normal, increased, hyperreflexia

Degree of clonus of ankles and knees

Resistance to passive movements of ankles, knees, hips
> 6 point scale ⇒ minimal, mild, moderate, moderately severe, severe, very severe

Global assessment of severity of disease
> 6 point scale ⇒ minimal, mild, moderate, moderately severe, severe, very severe
>   Yes/no questions
>   Do flexor spasms occur?
>   Is ankle clonus present?
>   Is ankle clonus sustained?
>   Is knee clonus present?
>   Is knee clonus sustained?
>   Change in clinical impression
>   5 point scale ⇒ worse to marked improvement
>   Overall spastic state
>   Daytime spasms
>   Night spasms
>   Muscle power/strength
>   Walking
>   Transfer activities
>   Dressing/undressing
>   Bladder function
>   Sleeping
>   Pain/stiffness
>   General dexterity
>   Speech/mentation

Patient assessment (baseline and 5 weeks)
> 4 point scale of none or little of the time to all of the time
>   Are you troubled by muscle spasms?
>   Does clonus occur?
>   Do your arms or legs feel painful?
>   Does stiffness trouble you?
>   Is your sexual performance impaired?
>   Are you hampered in your daily activities?
> 6 point scale of overall disability ⇒ minimal, mild, moderate, moderately severe, severe, very severe

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Table 5 summarizes the improvement in the various clinical parameters assessed. At Week 5 there were statistically significant changes in favor of baclofen for frequency of flexor spasms, tendon stretch reflexes of the knee, and resistance to passive flexion and extension. Regarding global assessment of severity of disease, after five weeks of treatment, the severity was reduced comparably in both the baclofen and placebo groups. Physician assessment of improvement in overall spastic state was statistically significant in favor of baclofen. Fifty percent of the baclofen showed improvement compared to 30% in the placebo group.

Table 5: Clinical changes baclofen versus placebo

	Week 3	Week 5
Mood	NS	NS
Frequency of flexor spasms	NS	+
Tendon stretch reflexes		
Left	+	+
Right	-	+
Resistance to passive movement		
Ankle flexion	+	+
Knee flexion	NS	+
Knee extension	NS	+
Global assessment		
Ankle clonus present and sustained	+	NS
Other factors	NS	NS
Patient self assessment		
Does clonus occur	-	+
Is sexual performance impaired	-	+
Other factors	-	NS
Physician's overall impression		
Overall spastic state	-	+
Daytime spasm	-	+
Night spasm	-	NS
Other factors	NS	NS

+ = statistically significant positive changes in favor of baclofen
NS = no significant change
- = not assessed at visit

It is unclear to me if that study would meet today's FDA criteria for approval. There was no confirmation of the results for the pivotal study. ICH numbers for population exposure for 6 months and 12 months were not met.

Supplemental analyses
Diagnostic and gender factors were analyzed in subgroup analyses. MS patients had better results with baclofen than the spinal cord patients. Both male and female MS patients tended to have uniform results. Spinal cord patients showed gender-related inconsistency on the variables clonus, overall spastic state, pain and stiffness. Females responded better on baclofen than males, with treatment differences from placebo similar to that of MS patients. The male spinal cord patients displayed a trend to do better on placebo in a number of variables. Due to the small sample size, it is not clear if this was due to chance or a real difference.

Of the 34 stroke patients who participated in the trial, only 13 were evaluable for efficacy. Six of the 13 were in the baclofen group and seven in the placebo group. No between-group comparisons were made statistically because of the small number of patients. The global impression indicated that none of the stroke patients improved. Five in the baclofen group and six in the placebo group stabilized, and one in each group deteriorated. Somnolence (56% on baclofen vs. 33% on placebo) and vertigo (13% on baclofen vs. 0% on placebo) were the most common adverse events in the stroke group.

Long-term Studies

Data from five open-label long-term studies under two protocols in 89 patients were pooled. Patients started with a two to three week washout period, and then were titrated on baclofen. Therapy duration at the time of NDA review ranged from 1 to 2 years. Effectiveness appeared maintained in patients who responded over this period without tachyphylaxis.

Supporting efficacy trials in the literature

The following studies describe early work with baclofen before it was approved in the United States. Early controlled studies with baclofen suggested a benefit of baclofen in alleviating spasticity in patients with multiple sclerosis or spinal cord injury, but had serious methodological limitations. They appear unacceptable as supportive studies on a regulatory standpoint.

Jones and associates (1970)

This small placebo-controlled crossover study was conducted in six spinal cord injury patients who had been treated for 1 to 3 months with diazepam 15mg to 30mg daily. Patients were randomly assigned to baclofen or placebo for 14 days. The initial dose of baclofen was 5mg t.i.d., increased by 5mg t.i.d. every three days to a maximum of 60mg daily. There was no mention of a washout period between treatments. Muscle tone was reduced in 5 of the 6 patients while on baclofen compared with placebo. No statistical analysis was conducted.

Pedersen and associates (1970)

Pedersen et al. conducted several early studies of baclofen. In a double-blind placebo-controlled crossover study in 15 patients with non-traumatic paraplegia, patients were treated for two periods of one week each with baclofen 25mg t.i.d. or placebo. Baclofen resulted in a significant reduction in the severity of spasticity compared to placebo. Ambulation was significantly better during the placebo period. In early open studies, an effect from baclofen was obtained in 88% of patients with spasticity or uncomfortable flexor or extensor spasms. In an open study of 69 patients treated more than 3 years with baclofen titrated to doses ranging 30-100 mg daily, improvement in spasticity was observed in 83% of cases. The most common side effects were fatigue and muscle weakness (43%) and sedation (9%). No statistical comparisons were reported.

Hudgson and Weightman (1971)

Hudgson and Weightman conducted a double-blind placebo-controlled crossover trial with baclofen in 23 patients (18 with multiple sclerosis). Patients were randomly assigned to baclofen or placebo in doses of 10 mg t.i.d. for ten days. A washout period of seven days separated the two treatment periods. Baclofen was significantly superior to placebo in mean changes in spasticity. There was a significant improvement from baseline in the placebo group but the improvement in the baclofen group was greater.

Cartlidge and associates (1974)

Cartlidge and associates studied 40 patients (MS and other conditions). This crossover study compared baclofen with diazepam given for four weeks each. Baclofen doses ranged 30-60 mg daily. A washout of one week separated the two treatment periods. Both drugs caused improvement in spasticity from baseline. No period effect was noted. Daytime sedation was the most common side effect with both treatments, with a higher frequency in the diazepam group.

Hedley and associates (1975)

Hedley and associates studied the effects of baclofen on spasticity and muscle spasms in 35 MS patients. This was an open label study, with baclofen dosing starting at 5 mg t.i.d., gradually increasing to either an effective dose or to intolerability. In an attempt to identify the placebo effect, the test drug was substituted for a week with placebo in patients who appeared to benefit from baclofen. If patients deteriorated, they were restarted on baclofen at their previous optimal dose. Those who did not deteriorate stopped treatment, were reassessed a week later and followed. There was a reduction of spasticity with baclofen in 16 patients (46%). When placebo tablets were substituted for those who improved, 10/16 (63%) were restarted on baclofen. The other six patients maintained their improvement on placebo.

From and Heltberg (1975)

From and Heltberg conducted a randomized, double-blind, crossover trial of baclofen and diazepam in 16 MS patients. Treatment periods consisted of two weeks of dose titration and two weeks of treatment. The two treatment periods were separated by a one-week placebo period. The average optimal daily dose of baclofen was ranged 30-120 mg. There was no significant difference between the two drugs in spastic limb ratings after four weeks of treatment. A marked improvement in flexor spasms was seen during treatment with both drugs. Sedation was a greater problem during diazepam treatment (69%) than during baclofen treatment (31%).

Duncan and associates (1976)

In this placebo-controlled, double-blind two-period crossover trial in 25 patients with spasticity secondary to spinal cord disease (11 MS), baclofen at doses 15-100 mg daily was compared to placebo. Patients were randomized to either baclofen or matching placebo for four weeks with a washout period before receiving the alternate treatment for four weeks. Twenty-two patients completed the study. The difference in spasm frequency between baclofen and placebo was statistically significant. Fifty-five percent of patients were significantly improved in resistance to passive movement during the baclofen treatment period compared to placebo.

Sachais and associates (1977)

This study apparently represents a subset of pivotal NDA study population, considering only MS patients. Out of 166 patients enrolled, only 106 were evaluable for efficacy. The optimal dose usually was 70-80 mg daily. Duration of treatment was 5 weeks. Evaluations were performed at baseline, at 3 weeks, and at 5 weeks. Baclofen showed significant improvement over placebo in flexor spasm pain and frequency, resistance to passive movement in ankle flexion, knee flexion, and knee extension, and tendon stretch reflexes. The overall spastic state, daytime spasms, nighttime spasms, and pain or stiffness improved significantly in patients treated with baclofen. The weighted mean scores for both patient populations showed that baclofen treated patients improved to a significantly greater degree than did those on placebo. Other clinical measures were unchanged in both treatment groups. Somnolence occurred in 71% of the baclofen group and in 36% of the placebo group. Laboratory and vital sign data showed no serious abnormalities.

D.   Efficacy Conclusions

The efficacy for this new dosage form of baclofen is supported by cross-reference to the original baclofen NDA. No new efficacy study was conducted. Baclofen is currently indicated for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. Labeling states that patients should have reversible spasticity. Labeling also states that baclofen may also be of some value in patients with spinal cord injuries and other spinal cord diseases. Baclofen is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders. The efficacy of baclofen in stroke, cerebral palsy, and Parkinson's disease has not been established.

VII.   Integrated Review of Safety

A.   Brief Statement of Conclusions

This 505 (b) (2) NDA adds little information to the well established safety profile of baclofen, since only two small bioequivalence studies were conducted. The safety profile of baclofen was established in NDA 17-581 and by the post-marketing experience. A new safety concern emerged from the bioequivalence studies: two patients (11%) developed oral petechiae after taking baclofen ODT with no water.

B.   Description of Patient Exposure

Forty-six healthy volunteers were enrolled in two bioequivalence studies in this 505 (b) (2) NDA. In study SP692, twenty-six subjects received two doses and two subjects received one dose of baclofen 20 mg ODT. In study SP741, seventeen subjects were exposed to a single dose of baclofen 20 mg ODT. Overall, 45 patients received at least one dose of baclofen ODT.

In NDA 17-581, 82 patients were exposed to baclofen for five weeks, at a dosage of up to 80 mg daily in the pivotal phase III study. In addition, 94 patients participated in phase 2 studies, and 43 patients in phase one studies. I could not establish how many of the patients participating in phase 1 and phase 2 studies were actually exposed to baclofen. Baclofen exposure in the original NDA is very modest compared to current FDA and ICH requirements, but these is a vast post-marketing experience with this drug in support of its safety.

C.   Methods and Specific Findings of Safety Review

In the original baclofen NDA (17-581) pivotal study, baclofen induced significantly more adverse reactions than placebo. Seven baclofen patients and three placebo patients were dropped due to adverse events, which were not detailed in the NDA. In laboratory tests, there were no trends of abnormal laboratory findings and no between-group differences. Vital signs showed no trends toward change.

Study SP692

A clinical laboratory evaluation, a physical examination, an ECG and vital signs were evaluated at screening and completion of the study. Given the timing of evaluation, sample size and the known efficacy/safety profile of baclofen, limited information was expected from this bioequivalence study. One subject withdrew due to an adverse event (anxiety/tremor). The investigator determined that the AE was unlikely to be related to the study drug, but the sponsor noted that tremor has been reported with baclofen tablets. No serious adverse event occurred.

The safety profile of baclofen disintegrating tablets was not different from that of marketed baclofen tablets. The most common adverse events (AEs) associated with the use of baclofen disintegrating tablets were sleepiness (21%), tiredness/fatigue (11%), dizziness/lightheadedness (11%), and headache (11%). Similarly, tiredness/fatigue (29%), and dizziness (21%) were the most common AEs with baclofen "conventional" tablets. All unexpected, unlabeled AEs were assessed by the investigator as unlikely or not associated with baclofen. They include arthralgia, anxiety, dysmenorrhea, hyperglycemia, and abnormal urine (bacteriuria) reported with baclofen disintegrating tablets; dependent edema (ankle edema from a sprain), myalgia (red, swollen biceps muscle), contact dermatitis (poison ivy), anemia, pyuria, and abnormal urine (bacteriuria, ketonuria, increased leukocyte esterase in urine) reported with baclofen "conventional" tablets (Table 6).

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Table 6: Treatment emergent adverse events in study SP692 (from table 18, page 138, clinical data summary)

Body System Adverse Event	BACOFLEX RapiTabs 20 mg (N = 28) n (%)	Baclofen 20 mg Tablets (N = 28) n (%)
Body As a Whole, General		
Fatigue	3 (11%)	8 (29%)
Asthenia	0	1 (4%)
Edema dependent	0	1 (4%)
Pain	0	1 (4%)
Central & peripheral nervous		
Dizziness	3 (11%)	6 (21%)
Headache	3 (11%)	0
Tremor	0	1 (4%)
Gastrointestinal		
Nausea	2 (7%)	2 (7%)
Anorexia	1 (4%)	0
Diarrhea	0	1 (4%)
Vomiting	1 (4%)	0
Metabolic & nutritional		
Hyperglycemia	1 (4%)	0
Musculoskeletal		
Arthralgia	1 (4%)	0
Myalgia	0	1 (4%)
Psychiatric		
Somnolence	6 (21%)	2 (7%)
Anxiety	1 (4%)	0
Insomnia	0	1 (4%)
Red blood cell		
Anemia	0	1 (4%)
Reproductive, Female		
Dysmenorrhea	2 (7%)	0
Skin & appendages		
Contac dermatitis	0	2 (7%)
Rash	1 (4%)	0
Urinary		
Urine abnormal	1 (4%)	3 (11)
Hematuria	2 (7%)	0
Pyuria	0	1 (4%)

Study SP741

As in study SP 692, a clinical laboratory evaluation, a physical examination, an ECG and vital signs were evaluated at screening and completion of the study. Given the timing of evaluation, sample size and the known efficacy/safety profile of baclofen, limited information was expected from this bioequivalence study. One subject withdrew for personal reasons prior to the baclofen ODT treatment period.

Few adverse events (AE) occurred in that study. In the baclofen ODT group, three subjects (18%) experienced three AEs. In the baclofen tablet group, three subjects (17%) experienced six AEs. All of the adverse events were mild in intensity. All subjects recovered from the adverse events (Table 7).

Table 7: Treatment emergent adverse events in study SP692 (from table 1, page 002, safety update submitted 9/25/03)

Body System Adverse Event	Baclofen 20 mg ODT (N = 17) N (%)	Baclofen 20 mg Tablets (N = 18) N (%)
Subjects with at least one AE	3 (18)	3 (17)
Body as a whole, general Pain	0	1 (6)
Psychiatric Dreaming abnormal	0	1 (6)
Red blood cell Anemia	1 (6)	0
Respiratory Pharyngitis	0	1(6)
Urinary Urine abnormal	0	*1 (6)
Pyuria	0	1 (6)
Vascular (extracardiac) Petechiae oral mucosa	2 (12)	0

A new safety concern emerged from the second bioequivalence study: in two subjects (11%) administered baclofen 20 mg ODT, petechiae were seen on Day 7 post-dose inside the right or left cheek. The events were described by the investigator as a few small red dots less than 1 mm in diameter at the line where the teeth meet. The investigator described the subjects as "cheek suckers." These adverse events were not considered to be related to trial medication by the investigator. Duration was respectively 34 and 35 hours. These petechiae were considered not related to the study drug by the investigator, and they resolved spontaneously. That adverse event was not reported when baclofen ODT was taken with water. Even though this adverse event was not considered as related to the study drug by the investigator, its occurrence only after administration of baclofen ODT with no water is, in my opinion, suggestive of a possible relationship to the study drug in the absence of another definite etiology (which was not provided by the investigator; the description of "cheek suckers" is purely speculative). The effect of multiple administrations of baclofen ODT on the oral mucosa has not been evaluated.

Current adverse drug reaction information

The following is the "Adverse Reactions" section of the current baclofen package insert:
"The most common is transient drowsiness (10-63%). In one controlled study of 175 patients,

transient drowsiness was observed in 63% of those receiving baclofen compared to 36% of those in the placebo group. Other common adverse reactions are dizziness (5-15%), weakness (5-15%) and fatigue (2-4%). Others reported:

Neuropsychiatric: Confusion (1-11%), headache (4-8%), insomnia (2-7%); and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizure.

Cardiovascular: Hypotension (0-9%). Rare instances of dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea (4-12%), constipation (2-6%); and rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency (2-6%); and rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar."

The above "Adverse Reactions" section is identical to the final printed labeling dated 11/77 in the NDA Summary Basis of Approval. No additional adverse reactions, precautions or warnings have been added to the initial package insert.

Abrupt Drug Withdrawal

Baclofen has been associated with a withdrawal syndrome, as is discussed in the Warnings section of the package insert. Patients have experienced a rebound increase in spasticity, hallucinations, seizures, confusion, and elevated temperature. FDA recently added a Boxed Warning and strengthened the Warnings section of the prescribing information of Lioresal Intrathecal (baclofen intrathecal), indicated for severe spasticity of cerebral and spinal origin. The warnings inform healthcare professionals about rare cases of intrathecal baclofen withdrawal that can lead to life threatening sequelae and/or death in patients who abruptly discontinue therapy.

Ovarian Cysts

A dose-related increase in incidence of ovarian cysts was found in the two-year rat study (control incidence 3.5%, compared to high dose incidence of 20.5%). Given these preclinical findings, a phase IV open-label study was conducted to evaluate if baclofen induces ovarian cysts in women. Ovarian cysts were found by palpation in about 4% of MS patients treated with baclofen for up to one year. In most cases, these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population. I also did a Medline search with the keywords "baclofen" and "ovarian". I got 6 hits, with no abstract relevant to the issue.

Clinical Review Section

Literature search

I did a clinical query in Medline with the keyword "baclofen", and the category "treatment". I got 145 hits. Most hits concerned intrathecal baclofen. One hit described the occurrence of hypotension and bradycardia associated with baclofen during general anesthesia (Sill JC et al. Anesthesiology. 1986; 64:255-8.) With the keywords "baclofen" and "safety", I got 24 hits, with one relevant: Garabedian SM and Ruffalo RL reported the adverse effects secondary to baclofen withdrawal (Drug Intell Clin Pharm 1985; 19:304-6).

Baclofen toxicity in patients with renal insufficiency

I also conducted a Medline search with the keywords "baclofen" and "toxicity". I got 86 hits. Some of the hits concerned descriptions of baclofen overdose, which I describe in the "Baclofen overdose" section below. Two papers concerned issues related to renal insufficiency.

Aisen et al. reported on a case of baclofen toxicity in a patient with subclinical renal insufficiency (Arch Phys Med Rehabil 1994; 109-11). These 39-year-old quadriplegic women developed over a 16-week period clinical signs of baclofen toxicity confirmed by progressively rising serum baclofen levels while on a conventional stable dosing regimen. During this period BUN and creatinine concentrations were normal and stable. However, creatinine clearance values were consistently low, suggesting renal insufficiency as the underlying cause. After a decrease in baclofen dosage, evidence of baclofen toxicity resolved. The author recommended that clinicians should be alert to signs of evolving baclofen toxicity even in patients on an apparently stable regimen.

Dahlin PA and George J reported a case of baclofen toxicity associated with declining renal clearance after ibuprofen (Drug Intell Clin pharm 1984; 18:805-8). A 64-year-old male with an incomplete spinal cord injury had been taking baclofen 20mg t.i.d for 2 1/2 months without side effects. His BUN and serum creatinine rose after ibuprofen 600mg t.i.d was begun. The patient displayed baclofen toxicity, developing confusion, disorientation, bradycardia, and hypothermia. His blood pressure dropped and he complained of blurred vision. Ibuprofen discontinuation and fluid repletion corrected the renal indices. Rapid tapering of baclofen was accompanied by reversal of baclofen toxicity.

I review papers relating to renal toxicity in the elderly below.

Baclofen overdose

I also conducted a Medline search with the keywords "baclofen" and "overdose". I grouped the papers by topic.

Clinical presentation

Roberge et al. reported a case of supraventricular tachyarrhythmia associated with baclofen overdose (J Toxicol Clin Toxicol 1994; 3:291-7).

Nugent S et al. reported on cardiac abnormalities after baclofen overdose (J Toxicol Clin Toxicol 1986; 24:321-8). Cardiac conduction abnormalities and hypertension developed in a patient who ingested approximately 500 mg of baclofen. The patient also exhibited the more common

features of baclofen overdose including coma, respiratory depression, hypotonia, and hyporeflexia.

Ostermann et al. reported on one case of coma mimicking brain death following baclofen overdose (Intensive Care Med 2000; 26:1144-6).

VanDierendonck DR and Dire DJ reported on a case of ingestion of baclofen 300mg and ethanol leading to coma with return to previous state with supporting therapy (J Emerg Med 1999; 25:239).

Fraser AD et al. reported fatal baclofen ingestion, with a plasma concentration of 17mg/L (J Forensic Sci 1991; 36:1596-602).

Ghose K et al. reported on the complications of baclofen overdosage (Postgrad Med J 1980; 56:867-7). A 39-year-old female patient was admitted to the hospital about 12 hr after overdose ingestion of 450 mg of baclofen. On admission, she was comatose, flaccid, and in respiratory failure. Later she developed muscle twitching and had several epileptic fits. She was treated symptomatically and became conscious within 36 hr. However, approximately 65 hr after the overdose she developed sinus tachycardia which was successfully treated with oral propranolol. Plasma concentrations, as measured on days 2 and 3, were within the therapeutic range but the elimination half-life was prolonged.

Lipscomb DJ and Meredith TJ reported on a 57-year-old woman suffering from multiple sclerosis who took an estimated 1500 mg of baclofen. She became deeply unconscious with generalized flaccid muscle paralysis and absent tendon reflexes. Toxicological analysis confirmed the presence of baclofen together with small amounts of paracetamol (acetaminophen) and glutethimide. Supportive therapy, including assisted ventilation for 3 days, led to complete recovery; anticonvulsant drugs were necessary for the treatment of grand mal fits (Postgrad Med J 1980;56:108-9).

Paulson GW reported a case of a major overdose of Lioresal (Neurology 1976; 26:1105-6). A 29-year-old woman with known Huntington's disease took from 900 to 970 mg of Lioresal. She was admitted in deep coma with absent brain stem reflexes and without spontaneous respiration, and she required cardiovascular support. She continued to require intensive support for a total of 72 hours and had one seizure during the recovery phase. Her eventual recovery was complete. I summarized papers on Baclofen toxicity in the elderly below.

Withdrawal after overdose
Peng CT et al. reported on prolonged severe withdrawal symptoms after acute-on-chronic baclofen overdose (J Toxicol Clin Toxicol 1998; 36:359-63). A 42-year-old male receiving chronic baclofen therapy 20mg daily, attempted suicide by ingesting at least 800 mg of baclofen. He was found in coma 2 hours post-ingestion with depressed respiration, areflexia, hypotonia, bradycardia, and hypotension. Treatment with intravenous fluids, atropine, dopamine, and hemodialysis was associated with restoration of consciousness within 2 days but disorientation,

hallucinations, fever, delirium, hypotension, bradycardia, and coma developed during the following week.

Overdose in the pediatric population
Chapple D. et al. reported on two cases of baclofen overdose in siblings, presenting with respiratory depression (Pediatr Emerg Care 2001; 17:110-2).

Perry HE et al. reported on baclofen overdose in a group of adolescents practicing drug experimentation (Pediatrics 1998; 6:1045-8). A group of adolescents became symptomatic after ingesting 3-30 20mg tablets of baclofen during a party. Fourteen patients were taken to local hospitals; nine required intubation. In eight patients, symptoms were noted within 1-2 hours after overdose. The most common clinical findings included coma (7), hypothermia (6), bradycardia (5), hypertension (4), and hyporeflexia (8). Mean length of mechanical ventilation was 40 hours. Three patients had unifocal premature ventricular contractions. Two patients had tonic-clonic seizures. A single dose of activated charcoal was given to all patients. Drugs administered included nifedipine (1), flumazenil (1), naloxone (1), lorazepam (2), and phosphenytoin (2). All patients recovered and were discharged home within five days of ingestion. Serial serum baclofen levels were obtained in all intubated patients (range 0.049-6.0; normal, 0.08-40 μg/mL). Levels obtained 14 hours after ingestion showed a linear correlation with length of mechanical ventilation. Persistent symptoms were noted in some patients, despite non-detectable baclofen levels.

Cooke DE et al. reported on six acute baclofen overdose in children (Vet Hum Toxicol 1994; 36:448-50). Rapid onset of central nervous system depression with respiratory depression was present to a greater or lesser degree in all patients. Agitation, convulsions and ataxia were also seen. The entire cohort responded to supportive management. An accurate assessment of the quantity of drug ingested was not possible.

Toxicokinetics
Gerkin R et al. reported on the elimination kinetics following baclofen overdose (Am Emerg Med 1986; 15:843-6). The authors followed serial plasma baclofen concentrations in a woman who ingested more than 2g of baclofen in a suicide attempt. The plasma clearance of baclofen was characterized by first-order elimination kinetics with a half-life of 8.6 hours. The authors suggest that the persistent central nervous system depression after the return of plasma baclofen levels to the therapeutic range is best explained by delayed clearance of baclofen from the CNS. The patient made a full recovery with supportive care. No evidence of saturable elimination kinetics was found.

Anderson reported on the pharmacokinetics in baclofen (1230mg orally) overdose (J Toxicol Clin Toxicol 1984; 22:11-20). No increase in the plasma half-life of elimination of baclofen could be observed (t1/2 = 4.58 hours). On the contrary, the authors found an increased plasma clearance (0.368 l/kg) compared to the kinetics usually found in healthy subjects.

Management
Muller-Schwefe G and Penn RD reported that physostigmine may be useful in treating baclofen overdose (J Neurosurg 1989; 71:273-5). In three cases, intravenous physostigmine (2mg) completely reversed the respiratory depression and coma caused by baclofen. Cohen MB et al. reported that atropine appeared to be useful in treating overdose cases complicated by bradycardia and hypotension (Am J Emerg Med 1986; 6:552-3). Three hours after admission for ingestion of at least 300mg baclofen as a single dose, the patient became comatose and subsequently bradycardic, hypotensive, and hypothermic. A prompt increase in heart rate and blood pressure followed administration of 1 mg of atropine sulfate.

Ferner RE also reported on atropine treatment for baclofen overdose (PostGrad Med J 1981; 57:580-1).

D.   Adequacy of Safety Testing

I do not believe that the original baclofen NDA (17-581, approved in 1977) meets the current FDA or ICH standards for drug approval. However, there is a vast post-marketing experience with this drug, which has now a well established safety profile. This new 505 (b) (2) application relies on cross-referencing with the original baclofen NDA (17-581).

E.   Summary of Critical Safety Findings and Limitations of Data

This NDA provides limited additional information to the vast clinical experience with baclofen, since patients in the two bioequivalence studies received only one to two single doses of the new dosage form. A new safety concern emerged from the bioequivalence studies: two patients (11%) developed petechiae after taking baclofen ODT with no water. That adverse event was not reported when baclofen ODT was taken with water. Even though this adverse event was not considered related to the study drug by the investigator, its occurrence only after administration of baclofen ODT with no water is, in my opinion, suggestive of a possible relationship to the study drug, in the absence of another definite etiology. This adverse event does not preclude approval, but should be better characterized as a phase 4 commitment (especially after mutiple administrations).

In NDA 17-851 studies, the most common adverse event was transient drowsiness (10-63%). Other common adverse reactions were dizziness (5-15%), weakness (5-15%), nausea (4-12%), confusion (1-1 1%), hypotension (0-9%), headache (4-8%), and fatigue (2-4%).

The adverse events (AEs) reported with baclofen ODTs in the two bioequivalence studies, SP692 and SP741, were similar in nature and frequency to those reported with marketed baclofen 20 mg tablets. No serious AEs were reported. There was one single adverse dropout in Study SP692, for intermittent tremor and anxiety. The investigator determined that the AE was unlikely to be related to the study drug, but the sponsor noted that tremor has been reported with baclofen tablets. The safety profile of baclofen ODTs was not different from that of marketed baclofen tablets. The most common AEs associated with the use of baclofen ODTs were somnolence (13%), tiredness/fatigue (7%), dizziness/lightheadedness (7%), and headache (7%). Similarly, tiredness/fatigue (17%), and dizziness (13%) were the most common AEs with baclofen tablets.

VIII. Dosing, Regimen, and Administration Issues

The proposed dosing is the same as for the reference listed drug. Current labeling recommends individual titration, with a start at a low dosage, and gradual increase until optimum effect is achieved (usually between 40-80mg daily). The following dosage titration schedule is suggested in labeling: 5mg t.i.d. for 3 days; 10mg t.i.d. for 3 days; 15mg t.i.d. for 3 days; 20mg t.i.d. for 3 days. The total daily recommended dose is 80mg (20mg q.i.d.). The lowest dose compatible with an optimal response is recommended.

Two issues specific to the new dosage form are the food effect on drug absorption, and the effect of co administration with or without water on drug absorption. The sponsor was requested to address these issues at the pre-NDA meeting. I refer the reader to the biopharmaceutics review for assessment of this issue.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Current labeling does not address gender. No gender differences were observed in the phase III study of the Lioresal NDA (n=175). I also conducted a Medline search with the keywords "baclofen" and "gender". I got 14 hits, with no abstract relevant to the issue.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Current labeling does not address racial/ethnic differences. I conducted a Medline search, using the keywords "baclofen", "age" and "safety". I had 13 hits, mostly concerning the use of intrathecal baclofen. No hit addressed the specific issue of age effect on safety. Using the keywords "baclofen", "age" and "efficacy", I had 62 hits. No hit addressed the specific issue of age effect on efficacy. I did the same research with the keywords "baclofen", "age" and "safety", and "baclofen", "age" and "efficacy". I got not hit relevant to the issue. I also looked at safety in the geriatric population, as described below.

C. Evaluation of Pediatric Program

. The reference listed drug labeling states that safety and effectiveness have not been established in pediatric patients below the age of 12. In addition, my review of the summary basis for approval and my brief review of NDA 17-581 suggests that one single patient under age 18 was exposed to baclofen in the drug development program. I summarized reports of baclofen overdose experience in the pediatric population above.

D.   Comments on Data Available or Needed in Other Populations

<u>Pregnancy</u>

Current labeling lists "Pregnancy Category C". Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times the maximum dose recommended (MRD) for human use, at a dose which caused significant reductions in food intake and weight gain in dams. This abnormality was not seen in mice or rabbits. There was also an increased incidence of incomplete vertebral ossification in fetuses of rats given approximately 13 times the MRD, and an increased incidence of unossified phalangeal nuclei of forelimbs and hind limbs in fetuses of rabbits given approximately 7 times the MRD. In mice, no teratogenic effects were observed, although reductions in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 or 34 times the MRD. There are no adequate and well-controlled studies in pregnant women. Current labeling recommends that "baclofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus".

<u>Nursing Mothers</u>

RLD labeling states that it is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when baclofen is administered to a nursing woman.

<u>Geriatric Use</u>

Reference listed drug labeling does not provide any data on the safety and efficacy of baclofen in the elderly. Current labeling lists the generic statement that "in general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy".

I did a Medline search using the keywords "baclofen", and "elderly", I got 213 hits. I grouped articles by topic.

Baclofen toxicity in the elderly
O'Rourke et al. (BMJ 2001; 323:870) suggested that withdrawal of baclofen may cause confusion in elderly patients.

Choo YM et al. (Nephron 2000; 4:546-7) report a case of severe respiratory depression by low-dose baclofen given for hiccups.

Rubin et al. reported a case of reversible mutism possibly induced by baclofen (Pharmacotherapy 1999; 4:468-70).

Ryan DM and Blumenthal FS reported a case where dyskinesia were induced when baclofen treatment was first initiated (Arch Phys Med Rehabil 1993; 74:766-7.)

Liu HC et al. reported on a case of baclofen-induced frontal lobe syndrome in an 81-year-old patient, reversible after baclofen discontinuation (Paraplegia 1991; 29:554-6).

Yassa RY and Iskandar HL reported on two cases of baclofen-induced "psychosis" (J. Clin Psychiatry 1988; 49:318-20).

White WB reported the case of a 74-year-old woman who developed a profound CNS depression and respiratory depression, generalized hypotonia, sinus bradycardia, and urinary retention following an increase in baclofen dose (Arch Intern Med 1985; 145:1717-8). Cessation of baclofen therapy and the relief of the urinary obstruction improved mental status and normalized motor function within 24 hours. A withdrawal syndrome of agitation, hallucinosis, and convulsive activity persisted for eight days following discontinuation of the baclofen. The author suggests that patients with various forms of CNS disease may be at risk of serious CNS depression with even small therapeutic doses of baclofen.

Abarbanel J et al. reported a case of encephalopathy associated with baclofen (Ann Neurol 1985; 17:617-8).

Arnold ES et al. report one case of manic psychosis following rapid withdrawal from baclofen (Am J Psychiatry 1980; 137:1466-7).

Renal toxicity in the elderly
Bassilios et al (Nephrol Dial Transplant 2000; 15:715-6) reported baclofen neurotoxicity (confusion and agitation) in a chronic hemodialysis patient, after 4 days of treatment at 5mg/day. They also suggested that hemodialysis may be the appropriate treatment for baclofen toxicity.

Peces et al. also reported two cases of baclofen neurotoxicity in chronic hemodialysis patients (Nephrol Dial Transplant 1998; 13:1896-7).

Chen KS et al. reported on a series of nine patients who exhibited neurotoxicity after baclofen oral therapy (Ann Pharmacother 1997; 31:1315-20). The authors also reviewed seven additional cases from a literature search. Most patients in that paper received only small doses and short-term baclofen therapy. Altered consciousness was the major presenting feature. Severe acute complications, such as seizures and respiratory depression, were relatively uncommon among patients with severely impaired renal function. Abdominal pain was noted in five of our nine patients. Most patients showed clinical improvement after hemodialysis. The authors cautioned against any use of baclofen in patients with renal failure. Hemodialysis was effective in alleviating the clinical symptoms and shortening the recovery time.

Stroke

Hulme et al. reported on a double blind crossover trial of baclofen against placebo in elderly stroke patients which was discontinued because the drug produced an unacceptably high level of drowsiness (Eur J Clin Pharmacol 1985; 29:467-9).

In a subsequent study, baclofen 10mg was given orally to 12 elderly stroke patients, and drug concentrations measured from a series of plasma samples. A group of healthy subjects given the same dose in a previous study were used as controls. Elderly patients took longer to achieve peak plasma baclofen concentrations, but healthy controls had higher peak values and eliminated the drug more rapidly; areas under the curve were similar in the two groups. Simulations based on mean data suggested in that study that increased drowsiness in the elderly was probably not due to changes in baclofen pharmacokinetics.

Patients with Renal Impairment

There has been no specific study investigating baclofen in patients wit renal impairment. Reference listed drug labeling states that because baclofen is primarily excreted unchanged by the kidneys, it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function. As identified in my Medline searches, I found several reports of baclofen toxicity in patients with impaired renal function (see Baclofen toxicity in patients with renal insufficiency and Renal toxicity in the elderly).

Hepatic impairment

Baclofen is excreted primarily by the kidney in unchanged form. Therefore, hepatic impairment is not expected to necessitate any dose reduction. Reference listed drug labeling does not address hepatic impairment.

X.   Conclusions and Recommendations

A.   Conclusions

NDA 21-589 is for a new dosage form of baclofen tablets (orally disintegrating tablets). The proposed indication is the same as that of the reference listed drug. The safety and efficacy of baclofen 10mg and 20mg tablets have been established in NDA 17-851. The new dosage form is proposed as bioequivalent to the reference listed drug (see biopharmaceutics review), and the benefits and risks of this new dosage form are not different from those of the reference listed drug.

B.   Recommendations

On a clinical standpoint, I recommend approval of this NDA.

Clinical Review Section

I also recommend

This is however not a prerequisite for approval of this application.

Review and Evaluation of Clinical Data

|	
NDA (Serial Number)	**21-589**
Sponsor:	**Schwarz Pharma**
Drug:	**Baclofen Orally Disintegr. Tablets**
Proposed Indication:	**Spasticity**
Material Submitted:	**DMETS Consult**
Correspondence Date:	**3/18/03**
Date Received / Agency:	
Date Review Completed	**5/5/03**
Reviewer:	**Eric P. Bastings, MD**

1. Introduction

In the ongoing review of NDA 21-589, the Division of Medication Errors and Technical Support (DMETS) conducted at DNDP request an analysis of the proposed proprietary names   to determine the potential for confusion with approved proprietary and established names as well as pending names. DMETS does not recommend the use of the names "

DMETS proposed comments to the sponsor are presented in section 2.

2. DMETS proposed comments to the sponsor

DMETS does not recommend the use of the proprietary names,
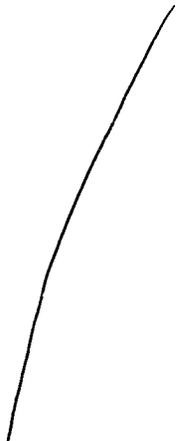
___3___ Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

_✓_ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

3. Comments

I generally agree with DMETS comments, with one exception.

I recommend the following comments to the sponsor (slightly modified from the DMETS proposed comments).

4. Comments to sponsor

We have completed the review of the proposed proprietary names for baclofen orally disintegrating tablet /   , in consultation with the Division of Medication Errors and Technical Support (DMETS). The proposed names are not acceptable, for the reasons discussed below.

3 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling
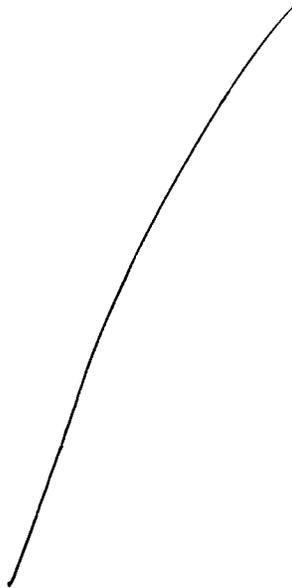
Eric P. Bastings, M.D.
Medical Reviewer

A. Oliva, MD _____

epb 5/5/03
cc:
HFD-120
NDA 21-589

Team Leader Note:

I agree with Dr. Bastings' review. The proposed names are unacceptable for the reasons
outlined in this review. Although we have already communicated the comments from
DMETS to the sponsor, these comments are much more informative and reflect the
review team's opinion, which are slightly different than those of DMETS (although the
conclusion is the same). Please convey them to the sponsor in their entirety.

/s/

Eric Bastings
5/7/03 02:29:28 PM
MEDICAL OFFICER

Armando Oliva
5/7/03 02:41:53 PM
MEDICAL OFFICER