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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-815/S-005

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 19-815 **SUBMISSION DATE:** April 12, 2001
ProAmatine^{R} (Midodrine HCl) Tablets
Supplement SMC-005

Shire Laboratories, Inc.
Rockville, MD **REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Waiver Request

SUBMISSION:

Supplement CMC-005 to NDA 19-815 dated April 12, 2001 provides for ProAmatine 10 mg Tablets as an additional strength to the existing ProAmatine Tablets 2.5 and 5 mg strengths.

In this supplement the sponsor is requesting a bio-waiver for the requirement of an in vivo bioequivalence study for this higher strength. To support the additional strength, the sponsor is submitting chemistry, manufacturing, and control data to demonstrate that ProAmatine Tablets, 10 mg is equivalent to ProAmatine Tablets, 2.5 and 5 mg. Comparative formulation and dissolution information are included in Attachment I.

The approved dissolution method and specifications for ProAmatine Tablets are as follow:

	PROAMATINE TABLETS
Apparatus	2, Paddle
Medium	0.1 N HCl
Dissolution Volume	900 ml
Rotation Speed	50 rpm
Analysis	[redacted]
Specification (Q)	Q=[redacted]% at 15 min

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information provided in NDA 19-815, Supplement SCM-005 for ProAmatine Tablets.

Although, the composition of the formulations for the 2.5, 5, and 10 mg ProAmatine Tablets are not proportional, OCPB/DPEI is of the opinion that a waiver for the requirement of an in vivo bioequivalence study for the additional strength of 10 mg for ProAmatine Tablets may be granted provided the sponsor provides additional comparative dissolution data in two additional media (i.e., pH 4.5 and 6.8 buffers) and corresponding F_2 values (if appropriate).

OCPB's above recommendation is based on the following overall information for this product:

- Previous PK studies showed linear kinetics for the 2.5, 5, and 10 mg doses of midodrine HCl
- The safety and efficacy of the 10 mg dose was evaluated in previous clinical trials
- The approved labeling recommends a dose of ProAmatine of 10 mg, 3 times daily
- Midodrine HCl meet the requirements of a highly soluble/highly permeable drug
- ProAmatine 2.5 and 5 mg Tablets are immediate release drug products and the comparative dissolution data for 2x5 mg and 10 mg tablets using the approved method showed that >95% is dissolved in less than 5 minutes

Please convey the Recommendation as appropriate to the sponsor.

/S/

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick J. Marroum, Ph.D. /S/

cc: NDA 19-815, HFD-110 (Mittal), HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

Attachment I

Includes

NDA 19-815 (SCM-005)

- Comparative Formulation Information
- Comparative Dissolution Data

Comparative Component Composition of ProAmatine® Tablets, 10 mg with ProAmatine® Tablets, 2.5 mg and 5 mg

Components	ProAmatine® (midodrine hydrochloride) Tablets					
	2.5 mg strength		5 mg strength		10 mg strength	
	Mg/tablet	% W/W	Mg/tablet	% W/W	Mg/tablet	% W/W
Midodrine hydrochloride	2.5(1)		5.0(1)		10.0(1)	
FD&C yellow# 6 Lake	---	---			---	---
FD&C Blue# 2 Lake	---	---	---	---		
Microcrystalline Cellulose, NF						
Corn Starch, NF						
Colloidal Silicon Dioxide, NF						
Talc, USP						
Magnesium Stearate, NF						
Total tablet Weight	**130.00**	**100.00**	**130.00**	**100.00**	**130.00**	**100.00**

(1)Theoretical weight based on Assay value of 100%
(2) Assay value limits
(3) Theoretical amount of coloring agent to be adjusted based on its dye content
(4)Theoretical amount of microcrystalline cellulose to be adjusted based on the amount of coloring agent used
(5) Theoretical amount of corn starch to be adjusted based on midodrine hydrochloride assay value

Comparative Dissolution Profile of ProAmatine Tablets, 10 mg and ProAmatine Tablets, 5 mg

Sample#	5 minutes		15 minutes		30 minutes	
	10 mg (% dissolved)	2x5 mg (% dissolved)	10 mg (% dissolved)	2x5 mg (% dissolved)	10 mg (% dissolved)	2x5 mg (% dissolved)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	**97.4**	**100.1**	**101.3**	**101.5**	**100.9**	**102.5**
Range						

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/s/

Angelica Dorantes
8/8/01 07:19:31 PM
BIOPHARMACEUTICS

Patrick Marroum
8/9/01 09:46:16 AM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I

NDA 19-815/SCM005 **SUBMISSION DATE** November 20, 2001

TYPE:	AMENDMENT TO SUPPLEMENT S-005
BRAND NAME:	ProAmatine®
GENERIC NAME:	Midodrine Hydrochloride
DOSAGE STRENGTH:	2.5, 5 mg oral tablet
SPONSOR:	Shire Laboratories, Inc.
PRIMARY REVIEWER:	Lydia Velazquez Kieffer, Pharm.D.
TEAM LEADER:	Angelica Dorantes, Ph.D. and Gabriele Robbie, Ph.D.

SUBMISSION:

The sponsor has submitted the above supplement as an amendment to the earlier supplemental drug application (S-005), NDA 19-815 dated April 12, 2001 and is intended to respond to the approvable letter dated August 13, 2001.

In this supplement, the sponsor is responding to OCPB's comment regarding the sponsor's in vivo bioequivalence waiver request for the 10 mg strength tablet. Our comment states that the sponsor will be required to provide additional comparative dissolution data in two additional media (i.e., pH 4.5, and 6.8 buffers) and corresponding F_2 values (if appropriate). In order to support their continued request for a biowaiver of the ProAmatine 10 mg strength, the sponsor has submitted comparative dissolution data located in Attachment I. Currently ProAmatine is approved in the 2.5 and 5 mg strength tablets.

The approved dissolution method and specifications for ProAmatine Tablets are:

Apparatus:	**II, Paddle**
Medium:	**0.1N HCl**
Dissolution Volume:	**900 mL**
Rotation Speed:	**50 rpm**
Analysis:	—
Specification (Q):	**Q = ◯% at 15 minutes**

Upon review of the submitted data certain information was still lacking and a complete review could not be made due to the following:

1. The rotation speed of Apparatus II (Paddle) used in their "Protocol for Comparative Dissolution Profile" was missing. It was unclear if the complete specifications used in the previous submission dated April 12, 2001 submission was utilized for this study.

2. It's unclear if the dissolution data for batch no. 293011 was repeated and only one data set was submitted.
3. The dissolution data for batch no. 293011 in 0.1N Hydrochloric Acid (Table 3) was missing and was necessary for full assessment of the biowaiver.

Upon communicating to the sponsor the data that was still missing, a new amendment to submission S-005 with new data was faxed to the Agency for review on March 14, 2002 and included in Attachment II. The recommendation below is based on the assessment of this submission (dated November 20th, 2001) and the amendment that was faxed on March 14th, 2002.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information provided in NDA 19-815, Supplement SCM 005 for ProAmatine Tablets.

Data to support a waiver for the requirement of an in vivo bioequivalence study for the additional strength of 10 mg for ProAmatine is now complete and a waiver may be granted based on the overall information for this product.

Our recommendation for approval is based on:

- Previous PK studies demonstrated linear kinetics for the 2.5, 5, and 10 mg doses of midodrine HCl.
- The safety and efficacy of the 10 mg dose was evaluated in previous clinical trials.
- The currently approved label recommends a dose of 10 mg, 3 times daily.
- The comparability of dissolution profiles in 3 media between 2X5 mg versus 1X10 mg.

Please convey the Recommendation as appropriate to the sponsor.

/S/

Lydia Velazquez Kieffer, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. /S/
CC list: HFD-110: NDA 19-815; HFD-860: (VelazquezKiefferL, Dorantes A, MehtaM; MarroumP); CDER Central Document Room (Biopharm)

Appendix I

Dissolution Data from Submission SCM-005 dated November 20th, 2001

NYCOMED

Table 1: Raw Data of the Dissolution Tests at pH=4.5 with ProAmatine 5 mg Tablets #204011, 10 mg Tablets#293031, and #293011

pH-value = 4.5									
intervals	5 minutes			15 minutes			30 minutes		
batch no.	#204011	#293031	#293011	#204011	#293031	#293011	#204011	#293031	#293011
strength	2 x 5 mg	1 x 10 mg	1 x 10 mg	2 x 5 mg	1 x 10 mg	1 x 10 mg	2 x 5 mg	1 x 10 mg	1 x 10 mg
sample									
#1									
#2									
#3									
#4									
#5									
#6									
#7									
#8									
#9									
#10									
#11									
#12									
mean	95.0%	57.3%	64.3%	100.2%	95.9%	96.1%	100.1%	98.5%	97.9%
CV*									

*CV = coefficient of variation

NYCOMED

Table 2: Raw Data of the Dissolution Tests at pH=6.8 with ProAmatine 5 mg Tablets #204011, 10 mg Tablets #293031 and #293011

pH-value = 6.8									
intervals	**5 minutes**			**15 minutes**			**30 minutes**		
batch no.	#204011	#293031	#293011	#204011	#293031	#293011	#204011	#293031	#293011
strength	2 x 5 mg	1 x 10 mg	1 x 10 mg	2 x 5 mg	1 x 10 mg	1 x 10 mg	2 x 5 mg	1 x 10 mg	1 x 10 mg
sample									
#1									
#2									
#3									
#4									
#5									
#6									
#7									
#8									
#9									
#10									
#11									
#12									
mean	92.8%	58.8%	72.0%	98.3%	96.0%	96.8%	98.6%	98.4%	97.9%
CV*									

***CV = coefficient of variation**

NYCOMED

Table 3: Raw Data of the Dissolution Tests in 0.1 N Hydrochloric Acid with ProAmatine 5 mg and 10 mg Tablets

0.1 N Hydrochloric Acid						
intervals	**5 minutes**		**15 minutes**		**30 minutes**	
batch no.	**#204011**	**#293031**	**#204011**	**#293031**	**#204011**	**#293031**
strength	**2 x 5 mg**	**1 x 10 mg**	**2 x 5 mg**	**1 x 10 mg**	**2 x 5 mg**	**1 x 10 mg**
sample						
#1						
#2						
#3						
#4						
#5						
#6						
#7						
#8						
#9						
#10						
#11						
#12						
mean	**100.1%**	**97.4%**	**101.5%**	**101.3%**	**102.5%**	**100.9%**
CV*						

***CV = coefficient of variation**

Appendix II
Completed dissolution data faxed on March 14th, 2002

AMENDMENT #2 to S-005, NDA 19-815

Comment # 1:

Please provide the paddle speed in the dissolution profile protocol.

Response:

The dissolution studies were performed in Apparatus 2 at a paddle speed of 50 ± 1 rpm. This information can also be found on page 200 of the April 12, 2001 submission.

Comment # 2:

Provide the initial and repeat comparative dissolution profile data for batch 293011.

Response:

In our submission of November 20, 2001 on page 19 in the "Introduction" section we made the statement "Preliminary tests at pH=4.5 and pH=6.8 were conducted with the ProAmatine 10 mg tablet batch #293031 in full conformity to the Prior Approval Supplement. The 12 dissolution rates after 5 minutes had a percent coefficient of variation of CV= % in pH=4.5 medium and CV= % in pH=6.8 medium. Therefore, according to the requirements ... the comparative dissolution data was repeated for ProAmatine 10 mg tablet batch # 293011, which was also submitted in the Prior Approval Supplement."

Shire regrets that the above language was not very clear and led to the misunderstanding that the data on batch # 293031 was repeated. In fact what Shire intended to say was that since the CVs at 5 minutes for batch # 293031 were higher than %, another batch (# 293011) which had already been included in the original supplemental application was also used to obtain dissolution profiles at pH 4.5 and 6.8. Dissolution data on both the batches was provided in Tables 1 and 2 respectively. As can be seen the CV% were high at 5 minute but were less than % at 15 minute and 30 minute time points. The dissolution values were quite comparable at all the time points. As was pointed out in the submission that in the first few minutes the tablets tended to partially disintegrate resulting in variability at 5 minute. This variability was not present at 15 minutes resulting in almost complete (>90%) dissolution.

Comment # 3:

Provide the dissolution profile data for batch # 293011 in 0.1 N HCl.

Response:

A revised Table 3 with data on batch # 293011 is attached.

Table 3 (revised): Raw Data of the Dissolution Tests in 0.1 N Hydrochloric Acid with ProAmatine 5 mg and 10 mg Tablets

0.1 N Hydrochloric Acid									
Intervals	**5 minutes**			**15 minutes**			**30 minutes**		
Batch #	204011	293031	293011	204011	293031	293011	204011	293031	293011
Strength	2 x 5 mg	1 x 10 mg	1 x 10 mg	2 x 5 mg	1 x 10 mg	1 x 10 mg	2 x 5 mg	1 x 10 mg	1 x 10 mg
Sample									
#1									
#2									
#3									
#4									
#5									
#6									
#7									
#8									
#9									
#10									
#11									
#12									
Mean	100.1%	97.4%	95.6%	101.5%	101.3%	98.4%	102.5%	100.9%	98.5%
CV*									

*CV = Coefficient of Variation

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/s/

Lydia Kieffer
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PHARMACOLOGIST

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Patrick Marroum
3/27/02 02:42:59 PM
BIOPHARMACEUTICS