CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-983/S-012

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-983	**SUPPLEMENT:** SE6-012
NAME: Prostep® (Nicotine Transdermal System) 11 mg/day, 22 mg/day	
SPONSOR: Elan Pharmaceutical Research Group, 1300 Gould Dr, Gainesville, Georgia	
SUBMISSION TYPE: OTC Switch Supplement	**SUBMISSION DATE:** September 22, 1998
REVIEWER: Suresh Doddapaneni, Ph.D.	

SYNOPSIS

Elan has submitted the current supplement seeking OTC approval of the currently marketed Prostep® patch 22 mg/day and 11 mg/day. Because of potential safety problems with the currently approved formulation, Elan is proposing to substitute the current formulation with an alternate matrix adhesive transdermal system for use in the OTC environment. This formulation was previously approved by the Office of Generic Drugs (OGD) as part of the Sano Corporation (now Elan Transdermal Technologies) applications ANDA #'s 74-612 (21 mg/day), 74-611 (14 mg/day) and 74-645 (7 mg/day). This submission consists of clinical data assessing the suitability of Prostep® patch for OTC switch and in addition, it contains results of an *in vivo* single dose bioequivalence study comparing the original Prostep® 22 mg/day patch and Sano 29 cm^2 patch (21 mg/day) approved by OGD (study P123-1298). Prostep® 22 mg/day patch was found to be bioequivalent to Sano 29 cm^2 (21 mg/day) patch. *In vitro* dissolution data was submitted in support of approval of the Sano 14.5 cm^2 (11 mg/day) patch that would substitute for Prostep® 11 mg/day patch. The submitted dissolution data showed that the dissolution profile of the Sano 14.5 cm^2 patch was similar to that of Sano 29 cm^2 patch. Overall, it can be concluded that Sano 14.5 cm^2 patch and Sano 29 cm^2 patch can be substituted for the currently marketed Prostep® 11 mg/day and 22 mg/day patches.

RECOMMENDATION

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics Sano 14.5 cm^2 patch and Sano 29 cm^2 patch can be substituted for the currently marketed Prostep® 11 mg/day and 22 mg/day patches. Regarding the dissolution method and specifications for these products, sponsor can use the currently approved dissolution method but a decision on the final dissolution specifications is not made at this point. Currently, this issue is being discussed by appropriate personnel in the Agency and once a consensus is reached, final decision will be taken whether to keep or tighten the currently approved dissolution test specifications. The formulation switch does not affect the information presented in the pharmacokinetics section of the package insert and the current language can be retained.

/S/ 12/11/98

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist,
Division of Pharmaceutical Evaluation II

FT initialed by Ramana Uppoor, Ph.D.: /S/ 12/11/98
CC:

I. INTRODUCTION

Prostep® was approved for marketing as a prescription product as an aid to smoking cessation treatment in January of 1992. In April of 1996, Elan filed supplement for OTC switch of Prostep®. Because of potential safety problems associated with the patch in its current form (i.e., dislodging of the nicotine gel matrix from the backing membrane when it is opened and falling onto the ground with a potential for small children picking it up and putting it in their mouth), Elan withdrew the supplement and resubmitted the application with a modification to the Prostep® patch on November 10, 1997 (supplement). The modification involved the use of an inert "overliner membrane" to cover the nicotine hydrogel. During the review of this supplement, further interactions between the Agency and sponsor led to the withdrawal of supplement as well and Elan is now resubmitting the application with a proposal to substitute the Prostep® patch formulation with an alternate matrix adhesive transdermal system. **This formulation was previously approved by the Office of Generic Drugs (OGD) as part of the Sano Corporation (now Elan Transdermal Technologies) applications ANDA #'s 74-612 (21 mg/day), 74-611 (14 mg/day) and 74-645 (7 mg/day).** Both 14 mg/day and 7 mg/day patches are proportionally similar to the 21 mg/day patch (The three strengths differ only in size-29 cm^2 (21 mg/day), 19.3 cm^2 (14 mg/day), 9.7 cm^2 (7 mg/day)). A bioequivalence study was conducted in support of approval of the 21 mg/day patch. Acceptable dissolution testing data was submitted in support of approval of the 14 mg/day and 7 mg/day patches. It is this alternate generic formulation which is proposed for use in the OTC environment. Essentially, the same 21 mg/day patch that was approved by OGD as generic to Habitrol would be substituted for the currently marketed Prostep® 22 mg/day patch. Since both 14 mg/day and 7 mg/day patches approved by OGD are outside of the Prostep® 11 mg/day patch, a new size patch (14.5 cm^2-11 mg/day) is cut from this alternate formulation that would allow the subtitution of the Prostep® 11 mg/day patch. The new submission consists essentially of the same clinical data that was submitted in supplement S-012. In addition, it contains results of an *in vivo* single dose bioequivalence study comparing the original Prostep® patch 22 mg/day and Sano 29 cm^2 patch approved by OGD (study P123-1298). *In vitro* dissolution data was submitted in support of approval of the Sano 14.5 cm^2 (11 mg/day) patch that would substitute for Prostep® 11 mg/day patch as **Sano 29 cm^2 and Sano 14.5 cm^2 patches are compositionally similar.** The data submitted in support of ANDA's 74-612, 74-611, and 74-645 is also submitted in support of the current supplement. Since this data was reviewed already by Dr. Farahnaz Nouravarsani in the Division of Bioequivalence, Office of Generic Drugs, this data will not be reviewed again. A copy of Dr. Nouravarsani's review will be placed in the Division files (Division of Anesthetics, Critical Care and Drugs of Abuse) of this submission and where appropriate the reader will be directed to read Dr. Nouravarsani's review for further clarification. The formulations of Prostep® 22 mg/day, Sano 29 cm^2 and Sano 14.5 cm^2 are shown in the following table.

Table 1. Composition of Prostep® 22 mg/day, Sano 29 cm² and Sano 14.5 cm² (mg)

Component	Sano 29 cm²	Sano 14.5 cm²	Prostep® 22 mg/day
Nicotine USP			
Acrylic Adhesive Solution			
Silicone Adhesive Solution			
Total			

II. BIOEQUIVALENCY STUDY

Study Title: The Evaluation of the Pharmacokinetic Properties of Nicotine and Wear Properties of Nicotine Transdermal System in Healthy Volunteers.
Study No.: P123-1298 **Study Initiation Date**: 03/19/98
Clinical Site:
Analytical Site:

Adhesive Residue & Apparent Dose Released - Charles Betlach, Elan Transdermal Technologies, Miramar, FL 33025

Study Design:
Open label: Yes Single dose: Yes Cross over: Three-way Randomized: Yes
Washout period: One week Smoke Free Period: 24 hour pre-dose smoke free period
Patient Demographics:
Number: 28 (completed) healthy male and female volunteers
Age: *mean* 43 yrs *range* yrs
Weight: *mean* 155 lbs *range* lbs

Formulation:

Treatment	Dose	Strength	Batch size	Batch Number
Sano 29 cm²	21 mg	21 mg/day		NC8001111
Sano 22.88 cm²	21 mg	21 mg/day		97E01111
Prostep®7 cm²	22 mg	22 mg/day		DD4844

Analytical Methodology:

Labeling Claims: None

Objectives:

To evaluate the bioequivalence of two nicotine transdermal patches relative to Prostep®.

Results And Discussion:

Sano 29 cm^2 and Sano 22.88 cm^2 are two different transdermal systems that were evaluated for substitutability of the Prostep® patch. Sano 29 cm^2 contains a total dose of 46 mg in a surface area of 29 cm^2. Sano 22.88 cm^2 contains a total dose of 26.1 mg in a surface area of 22.88 cm^2. **It should be reiterated again that Sano 29 cm^2 patch is the formulation approved by OGD under ANDA 74-612 and it is this patch that the sponsor proposes to substitute for the prostep® patch.**

Nicotine Analysis

Figure 1 shows the mean nicotine plasma concentrations of Prostep® 22 mg/day, Sano 29 cm^2 and Sano 22.88 cm^2 patches. Table 2 shows the results of bioequivalence analyses for nicotine. Sano 29 cm^2 was bioequivalent to Prostep® with respect to both C_{max} and AUC. Ninety percent (90%) confidence intervals for the log transformed C_{max} and AUC (both AUC_{0-48} and $AUC_{0-\infty}$ which were within 10% of each other) parameters were within 80-125% limit. However, Sano 22.88 cm^2 was not bioequivalent to Prostep®. Although, confidence interval for log transformed AUC was within 80-125% limit, confidence interval for log transformed C_{max} was outside the 80-125% limit.

Table 2. Pharmacokinetic parameters of nicotine (mean (%CV)) and results of bioequivalence analysis of the transdermal patches- Prostep® and test patches (n=28 subjects).

Parameter	Sano 29 cm^2	Sano 22.88 cm^2	Prostep®	90% Confidence Intervals for Log Transformed Parameters	
				Sano 29 cm^2/Prostep®	Sano 22.88 cm^2/Prostep®
C_{max}, ng/mL	14.37 (36)	18.46 (44)	14.72 (40)	91-108	114-135
AUC_{0-48}, hour*ng/mL	254.85 (34)	248.17 (40)	236.76 (37)	100-116	97-112
#$AUC_{0-\infty}$, hour*ng/mL	276.36 (28)	279.10 (35))	261.84 (33)	100-115	97-112

The AUC extrapolated from time 48 hours to infinity was based on a literature estimate of 2 hours for the elimination rate constant due to the poor estimate from the individual subjects following patch removal in a number of cases.

Figure 1: Mean Nicotine Plasma Concentrations

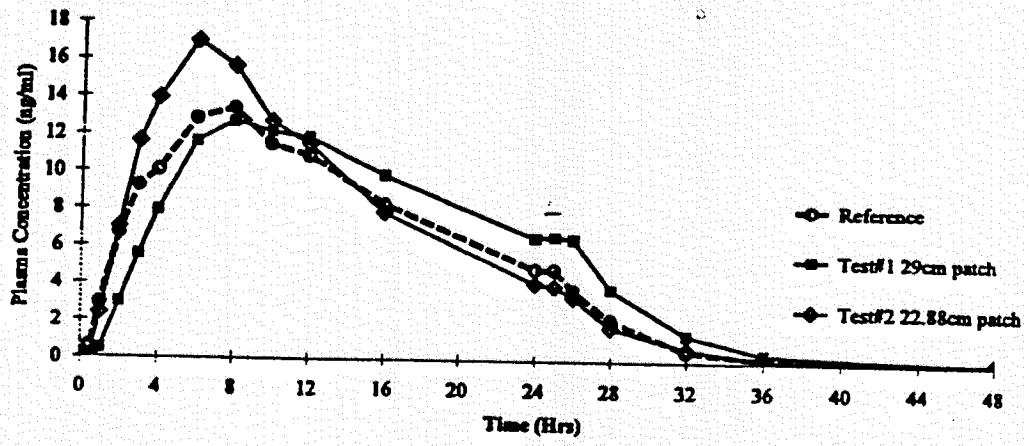
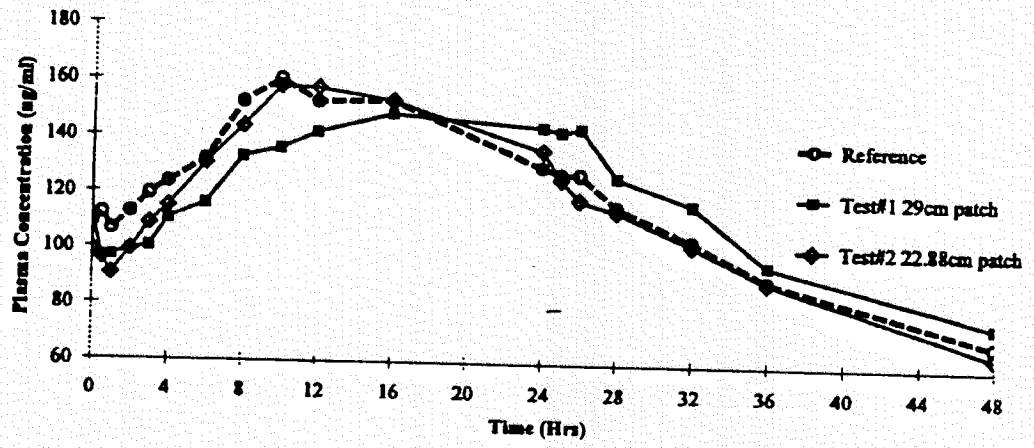


Figure 2: Mean Cotinine Plasma Concentrations



Cotinine Analysis

Figure 2 shows the mean cotinine plasma concentrations of Prostep® 22 mg/day, Sano 29 cm^2 and Sano 22.88 cm^2 patches. Table 3 shows the results of bioequivalence analyses for cotinine. Both, Sano 29 cm^2 and Sano 22.88 cm^2 were bioequivalent to Prostep® with respect to both C_{max} and AUC. Ninety percent (90%) confidence intervals for the log transformed C_{max} and AUC_{0-48} (extrapolated AUC constituted a significantly higher percentage of $AUC_{0-\infty}$ casting uncertainty on the use of this parameter in the analysis) parameters were within the 80-125% limit.

Table 3. Pharmacokinetic parameters of cotinine (mean (%CV)) and results of bioequivalency analysis of the transdermal patches- Prostep® and test patches.

Parameter	Sano 29 cm^2	Sano 22.88 cm^2	Prostep®	90% Confidence Intervals for log transformed parameters	
				Sano 29 cm^2/Prostep®	Sano 22.88 cm^2/Prostep®
C_{max}, ng/mL	170.89 (36)	175.59 (38)	173.43 (47)	93-112	95-114
AUC_{0-48}, hour*ng/mL	5688.55 (41)	5554.19 (40)	5637.64 (49)	95-113	94-111
*$AUC_{0-\infty}$, hour*ng/mL	8676.98 (50)	8556.47 (52)	8521.59 (58)	95-116	92-112

* Extrapolated AUC was calculated based on elimination rate constant calculated from post-patch removal samples

Residual Nicotine

All of the used nicotine patches (87) from the study (including patches applied to dropouts) were returned from the study site for analysis of residual nicotine content. Five of the Prostep® systems (worn by subjects) contained significantly lower residual nicotine than the remaining 24 systems, possibly reflecting dislodgement of the gel from the system upon removal. A mean of 19.54 mg was delivered by the Sano 29 cm^2 patch while the Prostep® patch delivered a mean of 17.34 mg.

Table 4. Residual nicotine data.

	Sano 29 cm^2	Sano 22.88 cm^2	Prostep®
Number of samples returned from study site	29	29	29
Number of samples included in the analysis	29	29	24
Potency (mg)	46.0	26.1	29.0
Residual Nicotine (mg)	26.46 ± 3.21	5.14 ± 1.79	11.66 ± 2.51
Apparent Dose (mg)	19.54 ± 3.21	20.96 ± 1.79	17.34 ± 2.51

Patch Adherence

Each patch was assessed at 2, 4, 6, 8, 10, 12, 14, 16, 22, and 23 hours to evaluate the adherence. Systems for which less than 10% of the area had lifted and/or were reapplied with pressure were classified as passed in terms of adherence. Units for which greater than 10% of the area had lifted and/or were secured using tape were classified as having failed. Once applied, tape remained applied until the patch was removed from the volunteer at the end of the 24 hour period and the system was considered to have failed at all subsequent time points. Where greater than 10% had lifted and pressure was applied, the patch was considered to have failed at the time point at which pressure was applied only. Only two of Sano 29 cm^2 patches failed at 23 hours, both having had tape applied at earlier time points showing that this patch has fairly good adherence properties.

Table 5. Transdermal system adherence data.

Time of Assessment (Hour)	Prostep®	Sano 29 cm^2	Sano 22.88 cm^2
2	1 (3.4)	0 (0.0)	0 (0.0)
4	1 (3.4)	0 (0.0)	0 (0.0)
6	0 (0.0)	0 (0.0)	2 (6.9)
8	1 (3.4)	0 (0.0)	2 (6.9)
10	0 (0.0)	0 (0.0)	5 (17.2)
12	0 (0.0)	1 (3.4)	5 (17.2)
14	1 (3.4)	1 (3.4)	5 (17.2)
16	1 (3.4)	1 (3.4)	5 (17.2)
22	1 (3.4)	2 (6.9)	8 (27.6)
23	4 (13.8)	2 (6.9)	12 (41.4)

Multiple Dose Bioequivalence Study

No multiple dose bioequivalence study was conducted comparing the original Prostep® 22 mg/day patch and Sano 29 cm^2 patch. However, a multiple dose (steady state) bioequivalence study was conducted on the Sano 29 cm^2 patch and it was found to be bioequivalent to 21 mg/day Habitrol patch (study P123-0595). This study was submitted originally to ANDA 74-612. Examination of this data shows that there is no significant accumulation in that successive 24 hour plasma concentrations after the administration of four successive patches were more or less similar (See reviews dated 5/4/97 & 9/18/97 for ANDA's 74-612, 74-611, and 74-645 completed by Dr. F. Nouravarsani). The trough (plasma concentrations 24 hours after the patch application and just before the application of the next patch) were 6.1, 5.1, 5.9, and 6.3 ng/mL at 24, 96, 120, and 144 hours, respectively.

Regarding the multiple dose data on Prostep®, it was stated in the original review for NDA 19-983 (see review dated January 6, 1992) that the accumulation ratio for the Prostep® patch was approximately 1.1 and steady state was achieved on the second day of dosing. Thus, it does not appear that both the Sano 29 cm^2 patch and Prostep® patch accumulate to a significant degree upon multiple dosing. Therefore, despite the lack of a direct head to head multiple dose bioequivalence study comparing the Prostep® and Sano 29 cm^2 patches, available individual steady state data on the Prostep® and Sano 29 cm^2 patches provides an assurance that there may not be any differential accumulation of either the Prostep® or Sano 29 cm^2 patches upon multiple dosing and that the single dose bioequivalence study

(P123-1298) comparing the Prostep® and Sano 29 cm^2 patches provides adequate evidence of the overall bioequivalence of the Sano 29 cm^2 and Prostep® patches.

III. DISSOLUTION TESTING

It should be noted that the sponsor submitted *in vitro* dissolution test data in support of approval of ANDA 74-611 (14 mg/day) and ANDA 74-645 (7 mg/day) after linking the 21 mg/day Sano patch with the currently marketed Habitrol 21 mg/day through bioequivalence studies in ANDA 74-612. The skin flux of nicotine was performed using human cadaver skin. A good point-to-point (level A) relationship was found between the *in vivo* absorbed fraction of nicotine and the dissolution data, or skin flux data (See reviews dated 5/4/97 & 9/18/97 for ANDA's 74-612, 74-611, and 74-645 completed by Dr. F. Nouravarsani). The dissolution method and specifications proposed were as follows;

Subsequent to this, the sponsor was requested by OGD to submit dissolution testing data, comparing their patch and the reference (Habitrol) patch using an appropriate drug release test (under nicotine transdermal system monograph) reported in the USP 23, supplement #5. The submitted dissolution testing data was found to be acceptable by Dr. Nouravarsani. Therefore, the currently approved dissolution method and dissolution specifications are as follows;

Apparatus: USP Apparatus 6, Shaft, Cylinder, and Vessel Assembly (USP 23)
Media: 137 mM NaCl
2.7 mM KCL
6.4 mM Na_2HPO_4
1.5 mM KH_2PO_4
Paddle Speed: 50 rpm
Sampling Times: hours
Dissolution Specifications: Amount dissolved at hours: between %
Amount dissolved at hours: between %

Therefore, the sponsor used the above dissolution method and dissolution specifications to generate dissolution data to support the approval of Sano 14.5 cm^2 (11 mg/day) patch. In order to compare the dissolution data between Sano 29 cm^2 and Sano 14.5 cm^2, data at two additional time points of hours were generated. The comparative dissolution test results in terms of % nicotine released are shown in Table 6. At the time points of hours, the reported mean values (12 units) for both patches are within the specified tolerances. No individual unit is outside the range. The % label claim released at 3, 6, 12, and 24 hours are shown in Table 7. Since the f_2 factor is 89.3 and no time point is

different by more than 15%, it can be concluded that the dissolution profile of Sano 14.5 cm^2 (11 mg/day) patch is similar to the Sano 29 cm^2 (22 mg/day) patch. Therefore, a waiver for biostudy for the lower strength Sano patch (Sano 14.5 cm^2) can be granted. Further, it should be noted that there was dose-proportional pharmacokinetics between the two original strengths of Prostep®. Therefore, Sano 14.5 cm^2 (11 mg/day) can be substituted for Prostep® 11 mg/day patch. It should be noted that the currently approved specifications are very wide and the submitted data shown in Table 6 does support tighter specifications. The final dissolution data submitted in ANDA's 74-612, 74-611, and 74-645 in support of approval of Sano 7 mg/day, Sano 14 mg/day, and Sano 21 mg/day also support tighter specifications than the specifications currently approved. Currently, this issue is being discussed by appropriate personnel in the Agency and once a consensus is reached, final decision will be taken whether to keep or tighten the currently approved dissolution test specifications.

Table 6. Dissolution test results in terms of % amount dissolved (mean (range) of 12 units).

Strength	Lot	3 hours	6 hours	12 hours	24 hours
Sano 29 cm^2	PS8004111	88.6	119.5	144.4	168.2
Sano 14 cm^2	NC8041111	87.2	115.2	142.7	165.4

Table 7. Dissolution test results in terms of % label claim (mean of 12 units).

Strength	Lot	3 hours	6 hours	12 hours	24 hours	$t_{\frac{1}{2}}$
Sano 29 cm^2	PS8004111	41.2	55.6	67.2	78.2	89.3
Sano 14 cm^2	NC8041111	40.6	53.6	66.4	76.9	

IV. CONCLUSIONS

1. The Sano 29 cm^2 patch approved by the Office of Generic Drugs has been found to be bioequivalent to 22 mg/day original Prostep® patch. Therefore, the Sano 29 cm^2 patch can be substituted for the currently marketed Prostep® 22 mg/day formulation.
2. Acceptable dissolution testing was conducted on Sano 29 cm^2 and Sano 14.5 cm^2 patches. Since the two strengths are proportional, the waiver of the *in vivo* bioequivalence study requirement for Sano 14.5 cm^2 patch (11 mg/day) is granted. Therefore, Sano 14.5 cm^2 (11 mg/day) patch can be substituted for the currently approved Prostep® 11 mg/day patch.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 19-983 **SUPPLEMENT:** SE6-012
NAME: Prostep® (Nicotine Transdermal System) 11 mg/day, 22 mg/day
SPONSOR: Elan Pharmaceutical Research Group, 1300 Gould Dr, Gainesville, Georgia
SUBMISSION TYPE: OTC Switch Supplement **SUBMISSION DATE:** September 22, 1998
REVIEWER: Suresh Doddapaneni, Ph.D.

Addendum to the Main Review

At the time of completion of the primary review for supplement SE6-012 to NDA 19-983 submitted on September 22, 1998, two issues were pending- (1) Finalization of the dissolution specifications for this product was defered to a later time pending discussions among Agency personnel relating to this issue (see Clinical Pharmacology and Biopharmaceutics review dated 12/10/98) and (2) Discussion of the findings of the audit of the bioequivalence study P123-1298 by Office of Compliance was deferred to later time as the audit was not complete at that time.

This addendum to the main review discusses these two issues;

(1) Sponsor should continue using the approved dissolution method (approved in generic product applications-ANDA's 74-612 (21 mg/day), 74-611 (14 mg/day) and 74-645 (7 mg/day)). However, the currently approved dissolution specifications (approved in ANDA's 74-612 (21 mg/day), 74-611 (14 mg/day) and 74-645 (7 mg/day)) based on the USP monograph for nicotine transdermal products are not acceptable as they are too wide. Based on the dissolution test data that was submitted on the two strengths that are under consideration for switch in NDA 19-983 supplement SE6-012, the following dissolution specifications are recommended to be adopted on an interim basis

Dissolution Specifications:

Dissolution specifications will be finalized once the sponsor submits dissolution test data

The sponsor was agreeable to this strategy when communicated during a teleconference on 12/18/98.

(2) Review of DSI's findings and sponsor's response to these findings showed that the bioequivalence data from study P123-1298 is of adequate quality to be used for approval of supplement SE6-012

RECOMMENDATION

The following dissolution specifications are recommended to be utilized for this product on an interim basis;

Dissolution specifications will be re-evaluated and finalized by the Agency once the sponsor submits, dissolution data on lots maintained on stability testing and from three production batches for each strength at release.

/S/ 12/22/98

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FT initialed by Ramana Uppoor, Ph.D.: /S/ 12/22/98