CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-983/S-012

MEDICAL REVIEW(S)

NDA
~~IND~~ #: **Medical Officer Review**

Drug:	19983 (SE6 #012) ProStep (Nicotine Transdermal System) 22mg/24 hours and 11mg/24 hours
Sponsor:	Elan Pharmaceutical
Proposed Indication:	Smoking Cessation (OTC)
Investigator:	Stuart Harris MD, Ph.D. Seaview Research, Miami, FL
Submitted:	23 Sep 1998
Reviewer:	E Douglas Kramer
Peer Reviewer:	Celia Winchell
CSO:	Indira Kumar
Dates:	23 Sep 1998 Submitted 24 Sep 1998 Received CDER 13 Nov 1998 Review Assigned 18 Nov 1998 Review Completed
File Name:	D:\DATA\NDAs\PROSTEP\REVIEWS\SE6012\PK012.doc

Action Required: None

Material Reviewed: Clinical study report (volume 27) and pharmacokinetic report (volume 23) for pharmacokinetic protocol 123-1298, "The Evaluation Of The Pharmacokinetics Of Nicotine And Wear Properties Of Nicotine Transdermal System In Healthy Volunteers—A Single Dose Study"

1 Background

The currently marketed design of the ProStep nicotine patch consists of a unique nicotine-containing hydrogel matrix which is held on the skin by an adhesive backing. The hydrogel is not strongly attached to the backing. During review of the initial OTC switch application (supplement 009), the reviewers became concerned that this hydrogel design might present a risk of nicotine toxicity resulting from pediatric oral exposure.

To address this issue, the sponsor elected to modify their solid-state generic Habitrol patch (made by Sano Corporation) so that it would be bioequivalent to ProStep. They would then use their existing OTC database in support of the switch.

The CMC data necessary to support the change of formulation is the subject of supplement 011. Supplement 012 contains prior OTC studies of ProStep and a new bioequivalence study # 123-1298, which is the subject of this review.

2 Study Design

This was a single-dose open label crossover pharmacokinetic study in healthy volunteers with a one week washout between treatments. The test products were Transdermal Nicotine System

(Sano Corporation, Lot 97E0111, 21.88cm^2) 21mg/day and Transdermal Nicotine System (Sano Corporation, Lot NC8001111, 29cm^2) 21mg/day. The reference product was ProStep 22mg/day (Lederle Laboratories, Lot DD4844). The proposed new product in supplement #011 is the 29cm2 patch. Plasma levels of nicotine and cotinine were measured predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 25, 26, 28, 32, 36, and 48 hours. Patch adhesion and irritation were checked periodically. Residual nicotine, adhesive, and irritation at the patch site were assessed at when the patches were removed.

Study subjects were normal volunteer smokers age with a plasma cotinine of >100ng/mL. Subjects were monitored for smoking abstinence at the study site from 24 hours prior to each patch application until the end of the study period 36 hours after dosing.

3 Study Objectives

3.1 Primary Objectives

Evaluate plasma nicotine and cotinine levels over 24 hours after single dosing

Evaluate bioequivalence between ProStep and one of the Sano patches

Evaluate the adherence of the transdermal nicotine systems

Assess the amount of adhesive remaining on the skin after a 24 hour usage period

Assess the degree of irritation

Determine and compare the amounts of nicotine released after a 24 hour period from the transdermal nicotine systems.

3.2 Secondary Objectives

Monitor the subjects for adverse events.

4 Study Results

Subjects were 22 men and 8 women. Their average age was 43 (range). Subject (a woman) was dropped from the study after period 1 for positive cocaine urinalysis. Subject (a man) was dropped from the study after study period 2 for the same reason. A total of 28 subjects finished the study. One of these subjects was excluded from the definitive pharmacokinetic analysis because he had no reportable plasma cotinine levels from hour 6 to 36 of study period 3 (22.88cm^2 patch).

5 Pharmacokinetic Results

The sponsor reports that bioequivalence to ProStep was demonstrated for the 29cm2 patch. See Dr.Doddapaneni's review for a detailed discussion of the pharmacokinetic results of this study. The following summary parameters are provided in the report:

Table 1 Mean Nicotine Log10 Transformed Pharmacokinetic Parameters

Parameter	Reference (ProStep 22mg/24hrs)	Test Product 29cm2 Patch	Test Product 22.88cm2 Patch
AUCall (ng/mL-hr)	224.09 (1.39)	241.00 (1.41) [100-116]	233.60 (1.40) [97-112]
AUC_1 (λz incl samples pre patch removal)	250.08 (1.35)	266.81 (1.31) [100-114]	266.94 (1.33) [100-114]
AUC_2 (λz using post removal samples only)	243.04 (1.35)	262.81 (1.34) [100-114]	306.23 (1.34)* [108-128]
AUC_3 (λz set to ln(2)/2)	226.98 (1.38)	242.48 (1.40) [100-115]	236.37 (1.40) [97-112]
Cmax (ng/mL)	13.72 (1.46)	13.52 (1.43) [91-108]	16.98 (1.51)* [114-135]
C24 (ng/mL)	4.52 (1.44)	6.19 (1.36)* [124-151]	3.89 (1.37)* [78-95]

Table 3 of the sponsor's pharmacokinetic study report. Values are geometric mean (gsd) [90% CI vs reference]. * indicates significant differences compared to reference treatments.

Residual nicotine analysis and estimates of apparent dose from the different patches are shown in the following table:

Table 2 Residual Nicotine Analysis And Apparent Nicotine Dose

	Reference (ProStep 22mg/24hrs)	Test Product 29cm2 Patch	Test Product 22.88cm2 Patch
# of Patches Returned From Study Site	29	29	29
# of Samples Included In Analysis	24	29	29
Potency, mg (based on pre-study testing)	29.0	46.0	26.1
Residual Nicotine, mg	11.66±2.51	26.46±3.21	5.14±1.79
Apparent Dose, mg	17.34±2.51	19.54±3.21	20.96±1.79

Table 7 of the sponsor's pharmacokinetic study report.

The report notes that 5 of the returned ProStep patches were not included in the above analysis because they were found to contain "significantly lower residual nicotine than the remaining 24 systems, possibly reflecting dislodgment of the gel from the system upon removal."

6 Safety

No deaths or serious adverse events were reported during this study. A total of 12 adverse events were reported by 9 subjects. Five events were reported for the reference product. Two events were reported for the 29cm^2 patch and 5 events were reported for the 22.88 cm^2 patch. All events were mild in severity. Events considered drug related were pruritis at patch site (7 reports by 5 subjects), headache (2 reports), and sleepiness (1 report). Phlebitis and neck pain (1 report each) were considered not related to study drug. Among reports of pruritis, 3 occurred with the reference treatment and 2 occurred with each of the test formulations.

Patch adhesion was checked every 2 hours for 16 hours and at 22 and 23 hours following application. Lifting of >10% of the patch area was considered failure. Using this standard, 7 reference systems were considered to have failed, 12 of the 22.88cm^2 systems were considered to have failed and 2 of the 29cm^2 systems were considered to have failed.

Skin was evaluated for local irritation at the time of patch removal using the 6 point rating scale (0=no reaction, ½= slight redness, 1=slight redness, 2= erythema and elevation, 3=erythema, papules and small blisters, 4=marked swelling and blisters). Using this scale, 17 subjects had a measurable local skin reaction to the reference treatment(12 had slight redness, 5 had erythema and/or slight redness), 11 subjects had a reaction to the 29cm^2 patch (8 had slight redness, 3 had erythema and/or slight redness) and 8 subjects had a reaction to the 22.88cm^2 patch (5 had slight

redness, 2 had erythema and or slight redness, 1 had erythema and elevation). All reactions resolved by 12 hours.

No clinically significant changes in laboratory parameters were identified.

7 Assessment

The possibility of dislodgment of the hydrogel from the original ProStep patch is consistent with the sponsor's observation of possible dislodgment of the gel from used patches in this study. The data suggest that the 29cm2 patch (which appears to be the proposed marketed product in Supplement 011) may be less irritating and less likely to detach from the users skin than the reference ProStep product.

/S/ 12/3/98

E Douglas Kramer, MD
Medical Officer

/S/ 12/3/98

Célia Winchell, MD
Medical Team Leader, Drug Abuse

Medical Officer Labeling Review

NDA #:	19983 (Supplement SE6 #012)
Drug:	ProStep
Sponsor:	Elan Pharmaceutical Corporation
Proposed Indication:	Smoking Cessation (OTC switch)
Submitted:	23 Sep 1998
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File Name:	D:\DATA\NDAs\PROSTEP\REVIEWS\SE6012\label1.doc

Action Required: Forward to OTC

Material Reviewed: labeling in volume 1 of the NDA supplement

APPEARS THIS WAY
ON ORIGINAL

Background

Summaries Of Studies With Implications For Labeling

The ProStep OTC switch NDA is based on the following studies of ProStep:

Table 1 Eligible Subjects in ProStep OTC switch NDA studies

Study	Eligible Smokers
893 004 Sites= 1134	Rx usage; age>=18 appropriate to 22mg patch. Exclusions per Rx labeling (e.g. uncontrolled or accelerated hypertension, recent MI); Rx recommended 4 to 8 weeks. Telephone f/u at 1 week, visit at 1 month.
893 003 Sites=5	>=20 cig/day; >=5/10 motivation score;Placebo Controlled.
694 003 Sites=5	>15 cig/day; >=7/10 motivation score; Placebo Controlled
694 001 Sites=5	<15 cig/day; >=7/10 motivation score; Placebo Controlled
993 001 Sites=1	<20 cig/day; >=5/10 motivation score; Placebo Controlled
694 002 Sites=5	"OTC" usage; >15 cig/day; >=7/10 motivation score; Patches cost $21/box of 7.

The Low-intervention studies above (893 003, 694 003, 694 001, 993 001 and 694 002) specified **24 hour patch use** and a **fixed duration of treatment (6 weeks)**. **No step-down regimen** was tested.

Results of these studies are summarized below:

Table 2 Results of ProStep OTC Switch NDA Studies

Study	ProStep Quitters	Placebo Quitters	P-value
893 004 22mg Rx	1011/9271(11%)		n/a
893 003 22mg	34/401(8%)	18/401(4%)	.03
694 003 22mg	28/321(9%)	17/322(5%)	.12
694 001 11mg	35/315(11%)	16/317(5%)	.008
993 001 11mg	6/53(11%)	1/55(2%)	n/a
694 002 22mg "OTC"	33/315(10%)		n/a

Data taken by reviewer from the sponsor's study reports or the review of study 893003. Values are number (%) of enrolled subjects. CO-confirmed abstinence (weeks 3 to 6) was used in all studies except the Rx use study (where CO was not obtained). Values for the Rx use study are based on 4 weeks continuous self reported abstinence during the 6 month study. P-values are calculated by the reviewer (Chi square with continuity correction) except for study 993 001 where the number of abstinent subjects was too small. Abstinence figures for studies 893 003 and 694 003 were validated by the reviewer using the sponsor's CANDA submission.

The 22 mg strength appears to be effective in persons smoking 15 or more cigarettes per day (studies 893 003 and 694 003) while the 11mg is likely to be effective in persons smoking less.

Common Efficacy Statement

In an effort to control excessive promotional claims by OTC nicotine replacement products, the following general statement (which has come to be known as the "common efficacy statement") was developed. It was intended to be used by all products of this class to describe to describe the efficacy of their products in ways that were considered fair and unbiased. Although the contents of the self-help program could vary somewhat across the products, these materials should be consistent with the common efficacy statement:

(Product name) helps smokers quit smoking by reducing nicotine withdrawal symptoms. Many (product) users will be able to stop smoking for at least a few days, but many will start smoking again. Most smokers usually have to try to quit several times before they completely stop.

Your own chances of quitting smoking depend on how strongly you are addicted to nicotine, how much you want to quit, and how closely you follow a quitting program like the one that comes with with this product.

If you find you cannot stop or if you start smoking again after using this product, please talk to a health care professional who can help you find a program that may work better for you.

Labeling Submitted

The sponsor's submission includes "Final Printed Labeling" in section 3 of the NDA. This includes labeling for both 22 and 11mg per day strengths.

Patch backing

System pouches

Consumer information leaflet

Inner carton

Disposal unit

Action guide to staying smoke free

Audio cassette copy

Outer cartons for starter and refill kits

Items shown above in **Bold** are reviewed to determine which claims are supported by the sponsor's clinical trials and whether the labeling is consistent in a general way with the Common Efficacy Statement developed for OTC nicotine replacement products.

Consumer Information Leaflet

The consumer information leaflet is inconsistent with the sponsor's clinical studies in the following ways: Page: 4
The sponsor's OTC studies support the use of the 22mg patch in those smoking 15 or more cigarettes per day and the use of the 11mg patch in persons smoking less. In the proposed leaflet, the 22mg patch is indicated for those smoking 16 or more cigarettes per day. The OTC studies all used 6 weeks of treatment of a single strength. A Step-Down regimen was not tested. Note that although a Step Down is an option for Rx use, there are no successful clinical trials (either Rx or OTC) that use a Step Down regimen. Page: 4
The OTC studies did not test an option for less than 24 hour wear. Labeling used in these studies specifically recommended wearing the patch for 24 hours.

In addition to changing the above, it is recommended that the Consumer Information Leaflet be renamed to something that conveys the fact that this is the booklet that contains the instructions on how to use the product and who can use it safely. As the label now exists, it is unclear which of the 2 booklets and the audiotape are the actual instructions for proper use of the product.

Outer Cartons For Starter And Refill Kits

The sponsor's submitted Carton labeling is inconsistent with their OTC studies in the same way as the Consumer Information Leaflet. In addition to the issues raised in the discussion of the Consumer Information Leaflet above, the 22mg patch is label "Step 1" while the 11mg patch is labeled "Step 2" when, in fact a Step Down regimen was not tested. (The same type of labeling with the terms "Step 1" and "Step 2" also appear on the inner carton label.)

Consumer Guide To Staying Smoke Free

This booklet contains suggestions about how ProStep users can help themselves quit and motivational reinforcement for the quit attempt. The suggestions are generally acceptable, but the booklet appears to be overstated or overly reassuring in several areas. For example:

- Weight Gain (page 7) contains the statement, "if you are uneasy about gaining weight, consider this: smoking a pack of cigarettes is as bad for your health as gaining 40 pounds (Feel better?)" No citation is given for this claim.

  Acknowledging that many people gain weight from quitting smoking is certainly important. However, equating a specific weight gain with a specific amount of smoking should be discouraged. An alternative phrase might be the following: "if you are uneasy about gaining

weight, remember: Even if you gain some weight when you quit, you will still be healthier than before you stopped smoking"

- Avoiding Temptation (page 9) includes the statement: "for example, on that night out with friends you may want to avoid alcohol because it gives you a strong desire to smoke. Instead, try being the designated driver for the evening."

  A statement such as this is incomplete in troubling ways. While avoiding alcohol may be a good idea, as the statement says, it may equally important to avoid bars and restaurants where smoking is allowed. An alternative phrase might be the following: "for example, on that night out with friends you may want to avoid alcohol because it may give you a strong desire to smoke. Instead, try being the designated driver for the evening—and drive your friends to a nonsmoking restaurant."

  The corresponding phrase in the Nicotrol Taking Action Booklet is (Page 8) is: "Alcohol and coffee are usually strong triggers for smoking. Try to avoid alcohol because it weakens your willpower. After you quit you may feel nervous. Caffeine can make you even more nervous. You may want to try decaffeinated coffee and tea, water or caffeine-free soda." There is no suggestion here that a bar is an OK place to be for someone in the early stages of quitting smoking. Indeed, one of the tips in the Nicotrol Taking Action Booklet (Page 16) is: "**Avoid Stressful Situations.** And avoid smokers and places that tempt you to smoke." The message continues in the Nicotrol Staying Smoke Free Booklet (Page 7): "**Think Twice About Drinking.** Avoid the alcohol-cigarette link. Substitute alcohol-free beverages. Avoid bars for a while."

  The NicoDerm CQ Users guide, includes the following language about alcohol under "**TIPS TO MAKE QUITTING EASIER**: Within the first few weeks of giving up smoking, you may be tempted to smoke for pleasure, particularly after completing a difficult task, or at a party or bar. Here are some tips to get you through the important first stage of becoming a non-smoker." The first tip under the heading **Right after Quitting** is "During the first few days after you've stopped smoking, spend as much time as possible at places where smoking is not allowed." The third tip is, "Try to avoid alcohol, coffee and other beverages you associate with smoking." Once again, the language about alcohol does not suggest that a bar or the smoking section of a restaurant is a good place for people to be while they are quitting smoking.

- Your Quit Day (Page 10) contains the following statement attributed to the 1988 Surgeon General's report: "Your body is already starting a series of healthy changes that will continue for years. Within 20 minutes of quitting for example, your blood pressure drops to close to the level it was before your last cigarette. The temperature of your hands and feet should increase to normal"

  There is no similar language in either Nicotrol or NicoDerm labeling.

While it is important to encourage people to stop smoking, it is equally important not to overstate the case. Although I was not able to find information resembling this quote in the Surgeon General's report, the benefits listed here appear to be associated with reversal of acute pharmacologic effects of nicotine. These effects are not the major health benefits people get when they stop smoking. Alternative language might be: "Your body is already starting a series of healthy changes that will continue for years. Some of the effects of nicotine on your body will go away quickly. Over time, the effect of smoking on your risk of serious heart disease and lung cancer will also improve."

- Quit Day Plus 1 (continued) (Page 16) contains the following statements: "Your chances of having a heart attack decrease 24 hours after quitting" attributed to the Surgeon General's 1988 report and "Three years from now your risk of heart attack will be about the same as if you'd never smoked" attributed to the American Heart Association.

  I was unable to locate supporting documents for either of these statements. In the case of the statement from the 1988 Surgeon General's report, it seems a bit odd to me that the a statement such as this one would be found in a report dealing with Nicotine Addiction. In addition, mortality ratios from the CPS II conducted by the American Cancer Society and cited in the 1990 Surgeon General's report are shown below:

Table 3 Overall mortality ratios Among current and former smokers by sex and duration of abstinence at date of enrollment, ACS-CPS-II,

	Current smokers	Former Smokers (abstinent 3 to 5 years)
Males 1-20 cigarettes per day	2.22	2.03
Male >=21 cigarettes per day	2.43	2.25
Females 1-19 cigarettes per day	1.60	1.41
Females>=20 cigarettes per day	2.10	2.03

Taken from 1990 Surgeon General's Report, Chapter 3, Table 2, Page 78. Selected values. Calculated for a 4 year period of follow-up.

These figures show that the overall mortality ratio of ex smokers, while improved, is substantial for both men and women. In the absence of adequate documentation, statements such as these should be discouraged.

The closest comparable language in the Nicotrol Taking Action Booklet (Page 4) is "Your risk of heart disease returns to normal within 1 year." While this statement might be more accurate if the phrase "to normal" were changed to "toward normal" it is less concerning than the alternative proposed by Elan. The Surgeon General's 1990 report describes the available data on smoking cessation and the risk of CHD as follows: "The data are compatible with a rapid, partial decline in risk, followed by a more gradual decline reaching levels of never smokers after a prolonged period. The initial decline appears to occur within one year of

cessation or perhaps even less and constitutes a reduction of about one half or more of the excess risk associated with current smoking. The remaining decline in excess risk is more gradual, with the risks approaching those of never smokers only after a number of years of smoking abstinence." (Page 239-240). Elsewhere, this number of years is cited as 15 (Page 11)

- After A Week (Page17) contains the statement "Starting 2 weeks after you quit, your circulation improves and your lung function increases up to 30%" attributed to the 1990 Surgeon General's report.

  In this case, I was able to find what I believe to be the data supporting the statement about improvement in lung function in the cited reference. The study appear to be a study of the occurrence of respiratory symptoms such as coughing expectoration, shortness of breath and wheezing (1990 Surgeon General's report, chapter 7, pages 285-287. Total symptoms decreased at 1 month for quitters compared to non-quitters. In a second study by the same author, improvement in pulmonary symptoms was noted at 3 months. I could not find a statement about improvement in circulation. A more general statement is recommended to avoid over promising: "Many people who quit smoking will soon notice an improvement in their breathing. Your breathing should continue to improve the longer you are abstinent."

Finally, it should be noted that neither the "common efficacy statement" nor basic warnings are included in the proposed Consumer's Guide. This information is included in **both** the Nicotrol booklets and in the NicoDerm Users Guide. While there is no objection to having a booklet about quitting that is separate from the basic product instructions, I believe it is important that the essential information about the use of the product that is conveyed in the "common efficacy statement" and the product warnings be included in all materials accompanying these products, together with a clear statement about which other booklet contains the basic directions for use.

Audio Cassette

The audio cassette features actors talking about their experiences quitting in a "call-in" show format. There are no objections to the use of this format. I would note, however, that there are no instructions regarding the basic use of the product included on the tape. While it is unnecessary to repeat the instructions in their entirety on the tape, basic information such as the efficacy statement, the strength to use and the recommended duration of use should be included and the listener should be referred to the instruction booklet for further details.

The only point of concern regarding the current format concerns comments by the "Host" regarding the importance of using the patch regularly for the full 6 weeks not "a couple of weeks" as the host says on page 3.

Recommendations

The above comments should be shared with DODP.

/S/ 4/2/98

E Douglas Kramer, MD
Medical Officer

/S/ 12/3/98

Celia Winchell, MD
Medical Team Leader, Drug Abuse