patch or with both treatments. In contrast, cardiac arrhythmias were not observed with any other treatment. The 10 animals treated with Skoal exhibited no significant change in blood pressure or heart rate. Modest increases in blood pressures (19 mmHg systolic and 11 mmHg diastolic) and heart rate (34 beats per min) were seen with Nicoderm. Similar changes in blood pressures (26 mmHg systolic and 20 mmHg diastolic) and heart rate (27 beats per min) occurred following Habitrol. Maximum nicotine plasma levels were observed between 0 min and 10 min after ProStep, intact or dislodged, and were 9.8 μg/mL and 5.4 μg/mL, respectively. By comparison, peak nicotine plasma levels seen with Skoal, Nicoderm, and Habitrol were 0.12 μg/mL, 2.6 μg/mL, and 3.4 μg/mL. These results indicate that buccal exposure to ProStep, either the intact patch or the gel , could result in significant cardiovascular effects including arrhythmias. The addition of the overliner would not be expected to reduce the effects of exposure to the intact patch, and, as noted above, there is no data to support the contention that the overliner reduces the likelihood of the gel detaching from the patch during application or use.

Given the potential severity of poisonings involving ProStep, the appropriateness of greatly expanding access to this product via approving over-the-counter marketing is in question. The likelihood of expanded access, despite the product's current low market share, is great. Through materials provided to the Division of Drug Marketing, Advertising, and Communications, the agency has learned that Elan has entered into an agreement with Perrigo, a company which markets private label pharmaceuticals. The marketing materials developed by Perrigo indicate that there are plans to market this patch, for which Elan has requested a name change to "NicoPatch," as a low-priced, private label (e.g. CVS brand, Rite Aid brand) product. The proposed name has been rejected by the nomenclature committee based on the division's objections to this unique product being positioned to suggest that it is identical to those available.

Conclusions:

- **There is substantial evidence of efficacy for ProStep's original formulation when used under OTC conditions.**
- **No unexpected findings were observed in the adverse event database, but the high rate of dermatologic adverse events warrants departure from the language used on labeling for other products in the class, as this particular product carries a higher risk of dermatologic AE's than its competitors.**
- **Adequate evidence of bioequivalence has *not* been established because of flaws in the biopharm study; therefore there is a lack of substantial evidence of efficacy for the to-be-marketed formulation. It is likely, however, that bioequivalence could be established if the study were to be repeated using appropriate methods.**
- **The effect of the overliner on improving the integrity of the patch, if any, is not known.**
- **The suitability of this product for the OTC environment remains in question.**

Recommendation:

I recommend non-approval of this supplement.
Because the to-be-marketed formulation has not been shown to be bioequivalent to the formulation used in clinical trials, there is no substantial evidence of efficacy for the to-be-marketed formulation. However, it has been noted that there is every expectation that the two formulations are indeed bioequivalent, and could be shown to be if proper biopharm studies were conducted. Using this approach, Elan could ultimately establish the needed linkage between their to-be-marketed formulation and the formulation used in the clinical trials and thereby establish substantial evidence of efficacy in support of the switch to OTC marketing. However, the issue of public health risk vs. benefit of this OTC switch would not be altered if this pharmacokinetic linkage were established. **I recommend that a definitive determination be made of the suitability of the ProStep patch (with or without overliner) for OTC use so that Elan can determine whether or not to pursue additional biopharm studies to establish bioequivalence of the two formulations.**

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

MEMORANDUM

To: Cynthia G. McCormick, M.D., Director, HFD-170
From: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products
Date: 12/11/98
Re: NDA 19-983/S012
Elan Pharmaceutical Research Group
ProStep (Nicotine Transdermal System) 11mg/day and 22 mg/day
Rx-to-OTC Switch Supplement
Submitted 9/24/98

This memo will convey my agreement with the review team regarding the approvability of this application to switch ProStep (Nicotine Transdermal System) from prescription to over-the-counter marketing.

Administrative History

Please see my memo of 5/4/98 for a more complete summary of the complex administrative history of this product. Briefly, ProStep (Nicotine Transdermal System) was approved in 1/92 for prescription use as "an aid to smoking cessation for the relief of nicotine withdrawal symptoms." An efficacy supplement for Rx-to-OTC switch was submitted in 4/96. Review of the efficacy trials supported the switch. However, safety concerns related to the unique design of the patch were identified by agency review (see my memo of 5/4/98). The prescription ProStep transdermal system consists of a . This well contains a with nicotine. ProStep's design, unlike the other patches, lacks a mechanism to control the rate of nicotine release from the patch.

Data existed to suggest that detachment of the gel from the backing was not uncommon. After extensive discussion with FDA, Elan withdrew the supplement in 2/97 to allow time to improve the design of the patch to address these concerns. Elan chose to produce a nicotine gel disc,

The review team initially concluded that, due to flaws in study design, the modified patch had not been shown to be

bioequivalent to the original patch and could not be linked pharmacokinetically to the efficacy database. Elan submitted an additional study which did demonstrate bioequivalence. Notable in the data for this study were several instances of gel dislodgment occurring in the patches used by study subjects. In addition to the data in the supplement, the agency also reviewed data from an additional preclinical study performed by FDA's Office of Testing and Research. This study highlighted the potential for toxicity under conditions of accidental oral exposure. The supplement did not contain clinical or CMC data to demonstrate that the modification of the patch improved the safety. Therefore, although the pharmacokinetic portion of the supplement allowed linkage to the previously-accepted efficacy studies, the safety concern remained unaddressed.

On June 2, 1998, FDA presented Elan with the findings of the OTR preclinical study, and discussed with them by teleconference the review team's conclusion that the modified patch had not been shown to be an improvement over the original patch. Faced with possible non-approval of the supplement, Elan presented a novel proposal which resulted in the withdrawal of and the submission of the present supplement.

Elan's proposal

On August 7, 1998, FDA met with Elan to discuss replacing the ProStep gel disc patch with a formulation which is bioequivalent, linking it to the efficacy database, but uses a different design which is similar to the approved OTC patches.

Through a corporate acquisition, Elan has access to an approved nicotine transdermal system manufactured by Sano, Inc. (now known as Elan Transdermal Technologies). This product was approved on October 20, 1997 under ANDAs 74-612 (21 mg/day), 74-611 (14 mg/day) and 74-645 (7 mg/day), with Habitrol as the reference listed drug. The Sano patch incorporates the nicotine into the adhesive layer of the patch, much like Nicotrol or Habitrol. The dose is proportional to the size of the patch. The highest strength patch, 21 mg/24 hours, has been shown to be bioequivalent to the 21 mg

Habitrol. The other doses, 14 mg/24 hours and 7 mg/24 hours, were approved based on in-vitro demonstration of dose proportionality.

Elan revealed that they had conducted a preliminary study showing that the 21 mg Sano patch is *also* bioequivalent to the 22 mg ProStep patch. Initially, Elan hoped to market the 14 mg and 7 mg patches as well under the ProStep name and proposed to label the product for use in a three-step regimen (similar to Nicoderm or Habitrol). Several problems with this approach were pointed out. After discussion, Elan agreed to manufacture an 11 mg strength to link the available patch strengths to those used in the efficacy trials and to pursue marketing of the 22 mg and 11 mg strengths using labeling supported by the ProStep efficacy trials.

Elan then withdrew Supplement and prepared two supplements: one that would provide for the manufacturing change to the new formulation (S-011), and one that would contain the data to support OTC switch (S-012, the subject of this memo).

Unresolved issues from Supplement

The following issue were raised in the review of and warranted particular attention in the review of S-012

- **The proposed labeling contained instructions for use not supported by the efficacy database.**

Because the approval of S-012 depends on the same efficacy database, the labeling issues have not changed

- **The original ProStep formulation was associated with a higher rate of adverse dermatologic events than its competitors.**

Because the formulation has been changed, the problem of dermal irritancy of the original ProStep patch is no longer relevant. Dermal irritancy studies of the Sano patch were performed and reviewed for the ANDA, and these will form the basis of labeling recommendations for the new ProStep.

Issues addressed in the review of Supplement S-012

1. **Is the to-be-marketed formulation bioequivalent to the formulation used in the clinical trials, allowing linkage to the efficacy database?**

Supplement S-012 contained results of an *in vivo* single dose bioequivalence study, study P123-1298, comparing the original Prostep® 22 mg/day patch and the Sano 29 cm^2 patch (the 21 mg/day patch approved by the Office of Generic Drugs). To support approval of the Sano 14.5 cm^2 (11 mg/day) patch that would substitute for Prostep® 11 mg/day patch, *in vitro* dissolution data was as Sano 29 cm^2 and Sano 14.5 cm^2 patches are compositionally similar. This information was reviewed by Dr. Suresh Doddapeneni. Clinical Pharmacology and Biopharmaceutics reviewer. In addition, the data submitted in support of ANDAs 74-612, 74-611, and 74-645 was also submitted in support of the current supplement. This data was reviewed by Dr. Farahnaz Nouravarsani in the Division of Bioequivalence, Office of Generic Drugs at the time of the ANDA review.

Data in support of substituting the 21 mg Sano patch for the 22 mg Prostep patch: The bioequivalence study reviewed by Dr. Doddapaneni 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). 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. 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.

According to Dr. Doddapaneni's review, 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. Elan plans to market the 29 cm^2 formulation.

Dr. Doddapaneni noted that 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. Dr. Doddapaneni's 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 similar. Furthermore, data from the original Prostep NDA show that the accumulation ratio for the Prostep® patch was approximately 1.1 and steady state was achieved on the second day of dosing. Thus, Dr. Doddapaneni concludes that both the Sano 29 cm^2 patch and Prostep® patch can be dosed repeatedly without significant accumulation. For this reason, Dr. Doddapaneni concluded 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.

Data in support of substituting the 11 mg Sano patch for the 11 mg Prostep patch: The approved ANDAs include doses of 21 mg, 14 mg, and 7 mg. However, to provide a substitute for the 11 mg patch used in the Prostep clinical trials, a patch delivering 11 mg/day was needed. Because the patches are cut from a sheet of nicotine-impregnated backing, resulting in a dose which is proportional to surface area, the ANDAs for the 14 mg/day and 7 mg/day patches were based on *in vitro* dissolution test data, after the sponsor linked the 21 mg/day Sano patch with the currently marketed Habitrol 21 mg/day through bioequivalence studies in ANDA 74-612.

Based on the proportionality of dose to size of the patch, Elan developed a 14.5 cm^2 that is intended to deliver 11 mg/day. In this application, *in vitro* dissolution data was submitted in support of approval of the Sano patch that would substitute for the 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. Since the two strengths are proportional, Dr. Doddapaneni determined that it would be appropriate to grant a waiver of the *in vivo* bioequivalence study requirement for Sano 14.5 cm^2 patch (11 mg/day). He concludes that Sano 14.5 cm^2 (11 mg/day) patch can be substituted for the currently approved Prostep® 11 mg/day patch.

In summary, 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.

2. Is the proposed manufacturing change acceptable?
The manufacturing supplement, SCM-011, was reviewed by Ms. Juanita Ross, who concluded that "from the CMC standpoint, adequate data is provided and all issues are addressed." Facilities have been inspected and are acceptable. The manufacturing supplement was recommended for approval by Ms. Ross and Dr. Albinus D'Sa, chemistry team leader.

The manufacturing change is acceptable.

3. Is the proposed labeling supported by the data?
The proposed labeling describes the 22 mg dose as "Step 1" and 11 mg dose as "Step 2." Smokers over 15 cigarettes/day are instructed to use Step 1 for 6 weeks and told that 2-4 weeks of step-down treatment is optional. Lighter smokers are instructed to use Step 2 for 6 weeks.

The efficacy database does not support this labeling. A preliminary dose-ranging study conducted as part of the efficacy trials led the sponsor to determine that the 22 mg dose was preferable for heavier smokers (>15 cigarettes/day) and the 11 mg dose was preferable for lighter smokers. Subsequently, the efficacy trials which support this approval were conducted using the two different patch strengths as separate regimens, in separate studies, with distinct populations. The regimen used for both doses is 6 weeks at a single dose.

On review of the efficacy trials, the primary medical officer, E. Douglas Kramer, M.D., concluded that the efficacy of ProStep in the low intervention studies appears to be low, but it does appear to offer a consistent advantage over placebo. 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.

Because labeling for the other nicotine replacement products switched from Rx to OTC has, in some cases, relied on evidence taken from both the OTC switch program and the

original prescription trials and Rx labeling, it is important to note that Dr. Kramer's recommendations, based only on the OTC development program, differ from the regimens described in the approved prescription labeling for ProStep. ProStep's prescription labeling recommends use of the 22 mg/day patch for all patients except those weighing less than 100 pounds, for whom the 11 mg/day dose is recommended. An "optional weaning dose" (11 mg/day for 2-4 weeks) is included in the labeling for those who begin on 22 mg/day, but the clinical trials described in the label include two trials which used 22 mg/day without weaning and two which used weaning. (The trials differed somewhat in others aspects as well). *Only the fixed dose, "no weaning," Rx trials demonstrated superiority to placebo.* Therefore, neither the OTC program nor the existing prescription labeling seems to offer substantial evidence for using ProStep in a "step-down" fashion.

Furthermore, the proposed labeling refers to wearing the patch for either 24 hours per day or 16 hours per day (removing at bedtime). However, the Prostep clinical trials all used 24-hour wear; therefore there is no data to support a 16-hour wear option.

To be consistent with the design of the trials which provide the substantial evidence of efficacy, ProStep should be labeled not as a two-step regimen, but as two products, one for heavier smokers and one for lighter smokers. Consumers should be instructed to wear the patch for 24 hours.

4. **Is the labeling used on other products in this class appropriate to describe the risk of adverse dermatologic events with this formulation?**

To address this question, the reviews of dermatologic irritation studies which had been completed in the course of the approval of ANDA 74-612 were examined by Dr. Cynthia McCormick, Director, HFD-170. In these studies, the Sano patch was evaluated in a 21-day irritancy study which compared it to saline, sodium lauryl sulfate, and a competitor patch. The Sano patch was found to be less irritating than either sodium lauryl sulfate or the competitor patch. This suggests there is no need to emphasize the risk of skin reactions in the labeling of the new Prostep patch.

The labeling used on currently approved transdermal nicotine systems will be adequate to describe the risk of adverse dermatologic effects with this formulation.

Conclusions:

The 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 as bioequivalence has been demonstrated.

The manufacturing change is acceptable.

The labeling proposed requires modification prior to approval. To be consistent with the design of the trials which provide the substantial evidence of efficacy, ProStep should be labeled not as a two-step regimen, but as two products, one for heavier smokers and one for lighter smokers. Consumers should be instructed to wear the patch for 24 hours. The labeling used on currently approved transdermal nicotine systems will be adequate to describe the risk of adverse dermatologic effects with this formulation.

Recommendations:
Approval is recommended.

Food and Drug Administration
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products

Memorandum

Date: December 14, 1998

From: Cynthia McCormick, MD, Director Cynthia G. McCormick MD
Division of Anesthetics, Critical Care and Addiction Drug Products
ODE III, CDER

Subject: Prostep Action

To: Debra Bowen, MD
Director, Division of Over the Counter Drug Products
ODE V, CDER

Division File NDA #19-938 SE6-011 and SE6-012/DFS

This memorandum conveys and explicates for the file the basis for the Division of Anesthetics Critical Care and Addiction Drug Product's Approval action to be taken with concurrence from the Division of Over the Counter Drug Products on the Prostep Nicotine Transdermal System Supplement NDA 19-938 SE6-011 for a manufacturing change and SE6-012 for change to over-the-counter marketing of the product as an aid to smoking cessation.

Background

Prostep patch is a nicotine replacement product that was approved for prescription marketing in January 1992. The product has been, then, marketed for 6 years, gaining time and extent experience and has undergone three years of safety efficacy and usage testing in an environment that was intended to approximate OTC usage. Additionally, manufacturing changes submitted to the FDA in September 1998 (Supplement SCM-011) provided for a new nicotine imbedded transdermal patch delivering doses of 22 mg and 11 mg/24 hours of nicotine and shown to be bioequivalent to the original patch. The studies submitted to this supplement establishing the bioequivalence of the two products provide an effective bridge between the safety, efficacy and usage studies of the OTC environment and the newly developed patch. The basis

for the finding of bioequivalence between the former and currently approved patch is discussed in detail in Dr.Doddapaneni's review of the data.
The most important elements of the OTC switch supplement are summarized in this memorandum. The history of the various transformations of the transdermal system with the focus on safety concerns will not be further discussed since they have now been satisfactorily eliminated with the manufacturing changes submitted recently by the Sponsor.

Efficacy

The efficacy of Prostep transdermal system was demonstrated in the studies submitted to the original NDA. In support of this application for OTC marketing, four placebo controlled trials were conducted (two studying 22 mg/day and two studying 11 mg/day compared to placebo) in an effort to establish that the efficacy of the system is not lost in an environment in which concomitant behavioral support and counseling were not consistently provided. The studies provided use of this product under the conditions of normal use.

The four principal studies in this supplement submitted in support of its efficacy in the OTC marketplace are shown in Table 1.

TABLE 1

STUDY	DOSE	N	DESIGN
893-003	22 mg vs. PBO	802	Randomized-Double blind placebo controlled parallel x3 mos Heavy smokers
694-003	22 mg. vs. PBO	643	same
694-001	11 mg vs. PBO	632	Randomized, DB PC parallel X 3mos Lighter smokers
993-001	11 mg vs. PBO	108	same

The 22-mg/day studies recruited heavy smokers, and the 11-mg studies recruited lighter smokers. Exclusion criteria included previous cardiac disease, pregnancy, and lack of motivation or willingness to make the weekly visits. It has been argued that this degree of screening provides more than would be provided in the real world OTC environment, although clearly the lack of behavioral intervention simulates the real OTC scenario.

The largest of the four studies, 893-003 was a double blind, placebo-controlled study in which 802 heavy smokers (~20 cigarettes/day) were randomized to 22-mg nicotine/day or placebo. The first dose of the product was administered in a supervised environment however counseling and behavioral therapy was not

provided in all patients. The primary efficacy endpoint was abstinence from smoking. Success was defined as complete abstinence for weeks 3-6 with CO verification. The quit rates for both groups (22 mg, PBO) were disappointing (TABLE 2), however there was a statistically significant difference between treatment and placebo in this study both for reported abstinence and CO verification.

Study 694-003 was also an adequate and well-controlled study in heavy smokers (N=643) and was similarly designed. The results of this study, while even less convincing, were consistent in terms of there being a difference of similar magnitude between the treatment (22-mg nicotine/24 hours) and placebo. The results, while not statistically significantly different on both measures, did not contradict the first study.

The two controlled trials in less heavy smokers, comparing 11 mg/day patch with placebo produced more convincing results based on CO verified abstinence than on subject reported abstinence and was highly statistically significantly better in one study and borderline in the second. (Table 2)

TABLE 2

Dose	study	Reported Abstinence active	placebo	p-value (X^2)	CO Verified Abstinence active	placebo	p-value (X^2)
22	893-003	48/401 (12%)	22/401 (5%)	0.001	34/401 (7%)	12/401 (4%)	0.002
22	964-003	47/321 (15%)	33/322 (10%)	0.09	28/321 (9%)	17/321 (5%)	0.16
11	993-001	9/53 (17%)	4/55 (7%)	0.12	6/53 (11%)	1/55 (2%)	0.04†
11	694-001	59/315 (19%)	43/317 (14%)	0.08	35/315 (11%)	16/317 (5%)	0.005

†Fisher's exact test, per Dr.Permutt gives p=0.06

While the applicability of these four studies to the OTC market may be called into question because of the circumstances under which the trials were conducted, that is more restricted, they do provide assurance that the use of Prostep nicotine transdermal system provides greater likelihood of abstinence from smoking (for 4 weeks) than placebo in heavy smokers who use the 22 mg/day dose and in less heavy smokers using the 11 mg/day dose. The findings in these four studies provided sufficient evidence of efficacy in the OTC environment to justify approval of this supplement.

Safety

This supplement contains safety data from a total of 10,308 subjects exposed to Prostep 22 mg/day and 468 subjects exposed to 11 mg/day in prospective clinical trials. Serious adverse events reported in these trials were not unexpected for this population (refer to reviews by Dr. Kramer and Dr. Chin).

The incidence of poisonings described in Dr. Kramer's review of the poison control data is certainly a function of the previous design, now corrected, and it should be pointed out that while there had been a potential danger of accidental ingestion by children and pets with the previous patch, none of the reported cases had serious consequences.

Skin irritation has been reported, as common with nicotine transdermal patches. A skin irritation study was submitted in support of this patch, previously reviewed by the FDA (Subject of NDA 74-611, NDA 74-612, and NDA 74-645). The study was a 21 day cumulative irritancy study in 31 evaluable patients (43 entered the study initially). The study consisted of 4 arms, the NTS patch which is the subject of this NDA, a competitor patch, sodium lauryl sulfate .1% and 0.9 % Saline. The applications were made under four occlusive patches to skin sites in the paraspinal regions of each subject with random allocation of the patches to the skin sites. The applications lasted for 23-1/2 hours. Following removal sites were scored for reactions and new patches were applied to the same site on a daily basis for a total of 21 days. The reactions were graded on scales of "effect on superficial layers of skin" (an eight point scale ranging from 0—no reaction to 7—strong reaction extending beyond skin site) and on "effect on skin" (a six point scale ranging from A—slight glazed appearance to H—small petechial erosions and/or scabs). Scores were tested for each agent for each day of the study and mean scores were compared. An analysis of total and mean irritancy scores and time to removal of patch (specified when a score of 3 is achieved on the 8-point scale. On all of these measures the study patch (the new Prostep patch) was significantly less irritating than the active control and sodium lauryl sulfate. Analysis of these studies provides adequate assurance that the potential for serious skin reactions is limited.

A 4-Month Safety Update was submitted to this NDA supplement focusing on data from September 1994 until July 20, 1998. The safety update focuses on serious adverse events, US spontaneous reports from the ANDA Sano (current Prostep) patch 21 and 14 mg, as well as literature reports of adverse events.

One study performed during that period was a study of the effects of NTS on the developing fetus. In this study 25 pregnant women a(15 cigarettes/day) who decided to stop smoking during the middle of their second trimester, were evaluated for fetal outcome. In this study, one patient reported an infant with TGV (transposition of the great vessels), a second with possible premature labor (this patient actually resumed smoking during the study), a third with abdominal pain. These findings

were inconclusive and complicated by lack of controls, and the history of significant smoking history for the first two trimesters of pregnancy.

Bioequivalence

The linkage provided to bridge the usage, safety, and efficacy studies performed to evaluate Prostep in the nonprescription environment with the newly manufactured 22 mg and 11 mg/day patches in a homogeneous matrix were provided by the sponsor and are discussed in detail by Dr. Doddapaneni.

Summary

The sponsor has provided sufficient evidence to support the safety and continued efficacy of Prostep 22 and 11 mg./24 hour patches as an aid to smoking cessation in the nonprescription environment.

Action

Recommend Approval of SE6-012 for OTC switch with concurrence of the Division of Over the Counter Drug Products and with the final printed labeling (attached).

PATENT INFORMATION

U.S. Patent No. 4,946,853 assigned to Elan Transdermal, Ltd of Monksland, Athlone, County Westmeath, Republic of Ireland, a subsidiary of parent Company, Elan Corporation, plc of Lincoln House, Dublin, Republic of Ireland, which is also the parent Company of the present Applicant, issued August 7, 1990 and expires April 29, 2008, claims the nicotine formulation and use referred to in the above-referenced application.

Respectfully submitted,

Marla J. Church
Corporate Patent Counsel

EXCLUSIVITY SUMMARY for NDA # 19-983 **SUPPL #** 012

Trade Name NICOTINE TRANSDERMAL SYSTEM **Generic Name** _____

Applicant Name ELAN PHARMACEUTICAL RESEARCH CORPORATION **HFD-** 170

Approval Date DECEMBER 23, 1998

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /___/ NO /X/

   b) Is it an effectiveness supplement?

   YES /X/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE6

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac