CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89884

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
Date: April 6, 1998

ANDA #89-884, 89-885, 89-886
Drug Product: Nitroglycerin Transdermal System 0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr

ISSUE: Skin Irritation Study

Regulatory History:

Hercon first submitted these ANDAs for Transdermal Nitroglycerin in 1987. In 1993, they submitted new studies because they had revised the formulation. At the time of the re-submission, a skin irritation study was included. This study was reviewed by the bio reviewer and a number of comments were sent to the firm in a letter dated 8/18/94. The company responded to these concerns in an amendment submitted 12/8/94. The study and the firm's reply were not addressed in the subsequent reviews of the 10/96 and 11/96 amendments.

The original skin irritation study compared placebo (Hercon patch without drug product) to the Hercon Transdermal System. This was a repeated insult study that evaluated cumulative irritation over three weeks of three-times-a-week patch application. After a two week rest period, the Hercon patch was re-applied to test for contact sensitization. One half of the subjects had the RLD product applied instead of Hercon's product in the final challenge phase. Skin irritation was measured 24 and 48 hours after removal.

This study design is not the Test vs. Reference comparison which is relevant to generic drugs. Therefore, at the time of final review of the application, this deficiency was noted. The firm was informed that they would have to do another skin irritation study comparing Test vs. Reference. They expressed concerns about not being informed of this in a timely manner during the lengthy review process and pointed out that the only approved product (Mylan) had not done a study comparing Test vs. Reference either. Their primary concern was one of fairness. Because of the situation, an effort was made to determine whether the study which has been done could meet basic requirements of comparative safety.

Review of Scientific Information Available

Nitroglycerin transdermal products are known to be irritating to skin, causing both contact dermatitis and contact sensitization. Skin irritation is caused by the transdermal product itself and is enhanced when Nitroglycerin is present in the patch.

A. **Labeling**

The label of the reference listed drug and the proposed label for the Hercon product both describe dermatitis under the Adverse Reactions Section. The section reads as follows:

> "Allergic reactions to Nitroglycerin are also common, and the majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving Nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions and these reactions can probably occur in patients receiving drug by any route."
>
> *Medical Officer Note: Both products have identical labeling to warn about the possibility of skin reactions with the use of this product.*

B. **Inactive Ingredients**

1. The components of the Reference Listed Drug, Nitro-Dur, are derived from the PDR and the label submitted by Hercon. The transdermal system has four layers and a protective peel strip which is removed before application. These are:

a. A tan-colored backing layer (that is impermeable to nitroglylcerin;

b. A drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide and silicone medical fluid;

c. An (membrane that is permeable to nitroglycerin; and

d. A layer of hypoallergenic silicone adhesive.

The rate of delivery is dependent on the size of the patch. Each cm^2 of the applied system delivers approximately 0.02 mg/hr of Nitroglycerin. Thus:

a 10 cm^2 patch delivers approximately 0.02 mg/hr,
a 20 cm^2 patch delivers approximately 0.04 mg/hr, and
a 30 cm^2 patch delivers approximately 0.06 mg/hr.

2. The Hercon transdermal system consists of four components. These are:

1. Nitroglycerin
2. adhesive polymer (acrylic)
3. adhesive polymer (acrylic)
4. backing film

The full list of drug product components follows:

1. A diluted nitroglycerin acrylic adhesive polymer mixture.
2. Silicone treated release liner, polyester
3. backing film termed 269 clear coextruded film).
4. Silicone treated polystyrene release liner

The patch size for each strength differs from the Reference Listed Drug.

The 0.02 mg/hr patch size is 7.5 cm^2.
The 0.04 mg/hr patch size is 15 cm^2.
The 0.06 mg/hr patch size is 22.5 cm^2.

Medical Officer Note: While there are differences in the patch materials and size, the drug delivery is the same and the patch components are made of acrylic polymer which should convey similar irritation profiles for both products.

C. Skin Irritation Study

The skin irritation study conducted by Hercon and submitted in 1993 does not meet today's standards for a study comparing Test drug vs. Reference drug. However, the methodology of patch application, reading of skin irritation and scoring for irritation are acceptable, despite the relatively infrequent (Q 2 days) application of the test patch. The information derived from the study is summarized below.

SKIN IRRITATION STUDY
n=86*

*N=120; 34 withdrawals due to personal reasons or side effects

I. INDUCTION PERIOD (21 days)
Readings 24 and 48 hours after patch removal
Number of Subjects with Each Score as their Peak Erythema Score

Score	0	+	1	2	3	4
A - 24h	2	6	[illegible]	[illegible]	1	0
B - 24h	[illegible]	[illegible]	[illegible]	3	1	0
A - 48h	[illegible]	16	[illegible]	8	0	0
B - 48h	[illegible]	13	18	3	0	0

A = test active B = test placebo

Scores 0 = No evidence of any effect
+ = Barely perceptible
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright-red erythema with/without petechiae or papules)
4 = Severe (Deep-red erythema withhh/without vesiculation or weeping)

II. CHALLENGE PHASE (35 days)
Readings 24 and 48 hours after patch removal
Number of Subjects with Each Score as their Peak Erythema Score

24 Hour Reading							48 Hour Reading						
Score	0	+	1	2	3	4	Score	0	+	1	2	3	4
A	[illegible]	[illegible]	[illegible]	0	0	0	A	[illegible]	2	3	0	0	0
B	[illegible]	5	2	0	0	0	B	[illegible]	3	1	0	0	0
B	[illegible]	4	7	0	0	0	B	[illegible]	2	0	1	0	0
C	[illegible]	[illegible]	[illegible]	2	0	0	C	[illegible]	3	2	0	0	0

A = test active B = test placebo C = RLD active

The results of this study indicate that the Hercon Transdermal Nitroglycerin System is a mild to moderate irritant and that the transdermal system itself can cause mild irritation. The irritation is most marked 24 hours after removal of the patch and diminishes after 48 hours to mild irritation in the active patch and no to mild irritation in the placebo (patch only group). No measurements are reported immediately after removal of the patch. In general, these latter reactions tend to be the most intense.

Challenge application of either test placebo or test active resulted in no to barely perceptible reactions in the test placebo group and a mild reaction in the test active group. All reactions had disappeared by 48 hours after removal of the patches. The application of the reference active did not yield additional information. It led to no to mild reactions at rates similar to the test active. Since it was only applied once, the reaction evoked was due to components in the test product which were similar enough to the test product to prompt a memory response. There was no evidence of contact sensitization in any of the groups and erythema was the only reported symptom.

The scores reported included those who had withdrawn from the study for side effects. Their highest score was also included. While the number is small this could lead to dilution of the observed irritation since they may have withdrawn prior to reaching their peak reaction.

DISCUSSION:

The study conducted by Hercon and submitted in their 1993 re-submission evaluates the skin irritation potential of their transdermal nitroglycerin patch and the transdermal patch alone. This study demonstrates that the irritation potential of their product is linked to both the patch itself and the nitroglycerin. The irritation demonstrated is generally mild and resolves readily. There is no comparison to the Reference Listed Drug. However, given the composition of the two products, it is unlikely that the RLD would demonstrate sufficiently less irritation to make the products unequivalent in this characteristic. In addition, the product will be labeled so that the potential for contact dermatitis and sensitization is clearly identified.

CONCLUSION:

Hercon submitted a skin irritation study in 1993 prior to the adoption of new standards, by the Office of Generic Drugs, requiring studies which compare the test product vs. the reference product. Their application is coming to completion in 1998 when these new standards apply. In the interest of maintaining fairness, the Agency has reviewed information which is avaliable to the Office of Generic Drugs to guide such a decision. The information, which includes adequate product labeling, adequate similarity of transdermal patch components and a skin irritation study demonstrating only mild reactions to the product, is considered adequate to assure the Agency of safety of the test product due to the circumstances outlined above..

/S/

Mary M. Fanning MD MD
Associate Director of Medical Affairs
Office of Generic Drugs

Medical Officer's Consultative Review of ANDAs 89-884, 89-885, & 89-886

Date: January 12, 1988

SPONSOR: Hercon Laboratories Corp.
Plainfield, N.J.

DRUG: Nitroglycerin transdermal systems 5 mg/day (ANDA 89-884), 10 mg/day (ANDA 89-885), and 15 mg/day (ANDA 89-886).

CONSULTATION REQUEST: 12/4/87. Division of Generic Drugs (HFN-230).

MATERIAL REVIEWED: Clinical safety data, submission of 11/12/87.

The safety data in the submission of 11/12/87 consist of a repeat insult patch test for irritation and sensitization. The same study has been submitted to each of the ANDAs.

The study was conducted by the (The test material was the transdermal patch without nitroglycerin. A total of 197 subjects completed the study; 27 subjects dropped out for unrelated reasons.

During the induction phase, applications of the test patch were made to the same skin site on the inner upper arm of each subject for 24 hour periods three times weekly, for a total of nine applications. Each patch removal was followed by a 24 to 48 hour rest period. At 11 to 19 days after the induction phase a challenge patch was applied for 24 hours, and the site was scored for reaction at 24 and 48 hours after application.

Skin response was scored on the following scale:

0 = no effect
+ = minimal, faint, uniform, or spotty erythema
1 = pink, uniform erythema covering most of the contact site
2 = pink-red erythema visibly uniform in entire contact site
3 = bright red erythema with/without accompanying petechiae or papules
4 = deep red erythema with vesiculation or weeping

If a subject developed a 2 reaction, the next patch was applied to a new adjacent skin site. The patch site could also be changed at the discretion of the study director.

The maximum reactions that occurred during the induction phase were a + reaction in 14 subjects, a 1 reaction in 5 subjects, and a 2 reaction in 5 subjects. The only reactions that occurred with the first application were + reactions in two subjects. The + to 1 reactions were generally isolated and transient. The 2 reactions occurred after 4 to 6 days of applications to the same site, and did not recur in any subject after a change to a new site for the remainder of the induction period.

The sponsor states that the test product did not induce primary irritation, nor was there evidence of induced allergic contact dermatitis; however, in addition to the reactions during the induction phase, there was blistering in one subject after the challenge application.

Evaluation: It is felt that the study is adequate to show that primary irritation would not be expected under the proposed conditions of use, with each daily application to a new skin site. However, sensitization apparently did occur in one subject. Unless the sponsor can explain this satisfactorily, it is felt that the applications should not be approved.

(1st) M.D.

Phyllis A. Huene, M.D.

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