

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

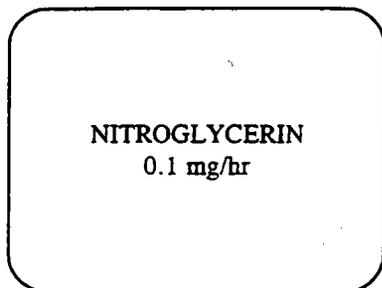
We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

2/6/98
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

NITROGLYCERIN TRANSDERMAL SYSTEM
0.1 mg/hr
PATCH LABELING





NDC 0378-9102-16



MYLAN

**NITROGLYCERIN
TRANSDERMAL SYSTEM**

0.1 mg/hr (4 cm²)

Each 4 cm² system contains 11.2 mg of nitroglycerin.
Approximate rapid release *in vivo* 0.1 mg/hr.
FOR TRANSDERMAL USE ONLY.
CAUTION: Federal law prohibits dispensing without prescription.

MYLAN PHARMACEUTICALS, INC.
Morgantown, WV 26505
Contents: 1 System

9102:1



9102:1

Instructions for Application

1. Bend both sides of clear peelable liner.
 2. The exposed sticky side of the patch.
 3. Apply sticky side of the patch to the chosen skin site.
 4. Remove remaining strip and press patch firmly in place with the palm of the hand.
 5. **APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.**
- Usual Dosage:** Each 24 hour period should include a patch on period of 12 to 14 hours, followed by a patch-free interval, unless otherwise directed by your physician. Store at 15-30 C (59-86 F). Do not refrigerate.

Pouch Face prints PMS 306 Blue,
PMS 200 Red and Black

Pouch Back prints Black

BLACK 200 RED

DIE-LINE

**Nitroglycerin
Transdermal
System
0.1 mg/hr**

Each 4 cm² system contains 11.2 mg of nitroglycerin. The inactive components are acrylic adhesive, polyolefin film, polyester release liner coated on one side with silicone and white ink containing titanium dioxide.

**MYLAN
PHARMACEUTICALS INC.
Morgantown, WV 26505**



MYLAN®

**NITROGLYCERIN
TRANSDERMAL SYSTEM**

0.1 mg/hr (4 cm²)

30 Systems

Each system contains 11.2 mg of nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent.

Rated release *in vivo* 0.1 mg/hr.

FOR TRANSDERMAL USE ONLY.

Patient: See instructions on back panel.

Usual Dosage: Each 24 hour period should include a patch-on period of 12 to 14 hours, followed by a patch-free interval unless otherwise directed by your physician.

STORE AT ROOM

TEMPERATURE

15°-30°C (59°-86°F)

DO NOT REFRIGERATE.

CAUTION: Federal law prohibits dispensing without prescription.

**NITROGLYCERIN
TRANSDERMAL SYSTEM
0.1 mg/hr
(4 cm²)**

NDC 0378-9102-93

Instructions for Application

1. Bend both sides of clear peelable liner.
2. Peel off one strip only of the clear liner. Avoid touching the exposed sticky side of the patch.
3. Apply sticky side of the patch to the chosen skin site.
4. Remove remaining strip and press patch firmly in place with the palm of the hand.
5. **APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.**

Usual Dosage: Each 24 hour period should include a patch-on period of 12 to 14 hours, followed by a patch-free interval, unless otherwise directed by your physician. Store at 15°-30° C (59°-86°F). Do not refrigerate.



N 3 0378-9102-93 5

LOT

EXP

M9102-93-30C:R1

**Nitroglycerin
Transdermal System
0.1 mg/hr**

Each 4 cm² system contains 11.2 mg of nitroglycerin. The inactive components are acrylic adhesive, polyolefin film, polyester release liner coated on one side with silicone and white ink containing titanium dioxide.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505



NDC 0378-9102-01

MYLAN®

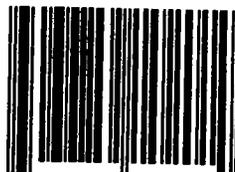
**NITROGLYCERIN
TRANSDERMAL SYSTEM**

0.1 mg/hr (4 cm²)

100 Systems

Each system contains 11.2 mg of nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent.

Rated release *in vivo* 0.1 mg/hr.
FOR TRANSDERMAL USE ONLY.
Patient: See instructions on back panel.



N
3 0378-9102-01 0

BLACK

200 RED

DATE LINE

LOT

LOT

EXP

M9102-01-100C:R1

(4 cm²)

0.1 mg/hr

**TRANSDERMAL SYSTEM
NITROGLYCERIN**

NDC 0378-9102-01

Usual Dosage: Each 24 hour period should include a patch on period of 12 to 14 hours, followed by a patch-free interval, unless otherwise directed by your physician.

**STORE AT ROOM TEMPERATURE
15°-30°C (59°-86°F)**

DO NOT REFRIGERATE.

CAUTION: Federal law prohibits dispensing without prescription.

Instructions for Application

1. Bend both sides of clear peelable liner.
2. Peel off one strip only of the clear liner. Avoid touching the exposed sticky side of the patch.
3. Apply sticky side of the patch to the chosen skin site.
4. Remove remaining strip and press patch firmly in place with the palm of the hand.
5. **APPLY IMMEDIATELY UPON REMOVAL FROM POUCH.**

Usual Dosage: Each 24 hour period should include a patch-on period of 12 to 14 hours, followed by a patch-free interval, unless otherwise directed by your physician.
Store at 15°-30°C (59°-86°F). Do not refrigerate.

How to use NITROGLYCERIN TRANSDERMAL PATCH for the prevention of angina

The Nitroglycerin Transdermal Patch is easy to use – it has a clear peelable liner, and a special adhesive that keeps the patch firmly in place.

Where to place the Nitroglycerin Transdermal Patch

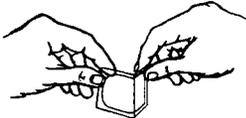
Select any area of skin on the body, EXCEPT the extremities below the knee or elbow. The chest is the preferred site. The area should be clean, dry, and hairless. If hair is likely to interfere with patch adhesion or removal, it can be clipped but not shaved. Take care to avoid areas with cuts or irritations. Do NOT apply the patch immediately after showering or bathing. It is best to wait until you are certain the skin is completely dry.

How to apply the Nitroglycerin Transdermal Patch

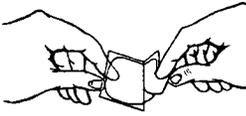
1. Each Nitroglycerin Transdermal Patch is individually sealed in a protective package. Open the pouch at the tear mark. Carefully remove the patch. The patch is printed with the wording 'Nitroglycerin' and the amount of nitroglycerin delivered each hour. The patch is attached to a clear peelable liner. The liner has a slit which divides it into two strips. Hold the patch with the wording facing away from you. The slit should now be facing toward you. Rotate the patch as necessary to place the slit in an up and down position.



2. Bend both sides of the clear peelable liner away from you at the slit.



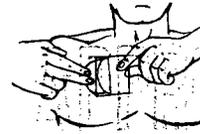
3. Slowly peel off only one of the strips of the clear liner. Do not touch the exposed sticky side of the patch.



4. Using the remaining strip as a "handle", apply the exposed sticky side of the patch to the skin. Press the sticky side on the chosen skin site and smooth down.



5. Fold back the unattached side of the patch. Grasp the remaining strip and remove it while applying the remainder of the patch to the skin. Press the patch on the skin and smooth down with the palm of your hand. Once the patch is in place, do not test the adhesion by pulling on it.



When Nitroglycerin Transdermal Patch is applied to your body, the nitroglycerin contained in the patch begins to flow from the adhesive surface through your skin at a uniform rate.

6. After applying the patch, wash hands to remove any drug.

7. At the time recommended by your doctor, remove and discard the patch.

8. Place a new patch on a different skin site (following steps 1 through 6) according to your doctor's instructions.

Please note:

Contact with water, as in bathing, swimming, or showering will not affect the patch. In the unlikely event that a patch falls off, discard it and put a new one on a different skin site.

Precautions:

The most common side effect is headache, which often decreases as therapy is continued, but may require treatment with a mild analgesic. Although uncommon, faintness, flushing, and dizziness may occur, especially when suddenly rising from the recumbent (lying horizontal) position. If these symptoms occur, remove the patch and notify your physician.

Skin irritation may occur. If it persists, consult your physician.

Keep these patches and all drugs out of the reach of children.

Important:

Your doctor may decide to increase or decrease the size of the patch, or prescribe a combination of patches, to suit your particular needs. The dose may vary depending on your individual response to the patch.

This patch is to be used for *preventing* angina, not for treating an acute attack.

**STORE AT ROOM TEMPERATURE 15° - 30°C (59° - 86°F).
DO NOT REFRIGERATE.**

Do not store outside of the protective package. Apply immediately upon removal from the protective package.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED JULY 1997
PL:NTG:R5



NTG:R5



**NITROGLYCERIN
TRANSDERMAL
SYSTEM**
0.1, 0.2, 0.4 and
0.6 mg/hr

DESCRIPTION: Nitroglycerin is 1,2,3-propanetriol trinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 227.09. The organic nitrates are vasodilators, active on both arteries and veins.

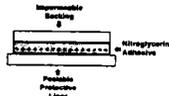
The nitroglycerin transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin.

The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm² of applied system delivers approximately 0.026 mg of nitroglycerin per hour. Thus, the 4-, 8-, 16- and 24 cm² systems deliver approximately 0.1, 0.2, 0.4 and 0.6 mg of nitroglycerin per hour, respectively. Each 4-, 8-, 16- and 24 cm² system contains 11.2, 22.4, 44.8 and 67.2 mg of nitroglycerin, respectively.

The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered approximately 11% of its original content of nitroglycerin.

Each system contains nitroglycerin in an acrylic pressure sensitive adhesive with a cross-linking agent to provide a continuous source of active ingredient. The nitroglycerin transdermal system comprises two layers as shown below. Proceeding from the visible surface towards the surface attached to the skin, these layers are: 1) a low density polyethylene backing layer that is impermeable to nitroglycerin and is printed with the name of the drug and strength; 2) nitroglycerin in an acrylic pressure sensitive adhesive. Prior to use, a peelable polyester release liner, which is coated on one side with silicone, is removed from the adhesive surface. Each unit is sealed in a foil-lined pouch. The inactive components are acrylic adhesive, polyolefin film, a polyester release liner coated on one side with silicone, and white ink containing titanium dioxide.

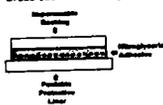
Cross section of the system:



CLINICAL PHARMACOLOGY: The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure. *Int J Clin Pharmacol Ther* 1978; 16: 101-107

to provide a controlled source of active ingredient. The nitroglycerin transdermal system comprises two layers as shown below. Proceeding from the vesicle surface towards the surface attached to the skin, these layers are: 1) a low density polyethylene backing layer that is impermeable to nitroglycerin and is printed with the name of the drug and strength; 2) nitroglycerin in an acrylic pressure sensitive adhesive. Prior to use, a peelable polyester release liner, which is coated on one side with silicone, is removed from the adhesive surface. Each unit is sealed in a foil-lined pouch. The inactive components are acrylic adhesive, polyolefin film, a polyester release liner coated on one side with silicone, and white ink containing titanium dioxide.

Cross section of the system:



CLINICAL PHARMACOLOGY: The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arterial relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Pharmacokinetics: The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow; known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but they are longer-lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. The dinitrates are further metabolized to (nonvasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide.

To avoid development of tolerance to nitroglycerin, drug-free intervals of 10 to 12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was less than that exhibited by the parallel group receiving placebo.

In healthy volunteers, steady-state plasma concentrations of nitroglycerin are reached by about two hours after application of a patch and are maintained for the duration of wearing the system (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

Clinical Trials: Regimens in which nitroglycerin patches were worn for 12 hours daily have been studied in well-controlled trials up to 4 weeks in duration. Starting about 2 hours after application and continuing until 10 to 12 hours after application, patches that deliver at least 0.4 mg of nitroglycerin per hour have consistently demonstrated greater antianginal activity than placebo. Lower-dose patches have not been as well studied, but in one large, well-controlled trial in which higher-dose patches were also studied, patches delivering 0.2 mg/hr had significantly less antianginal activity than placebo.

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It is reasonable to believe that the rate of nitroglycerin absorption from patches may vary with the site of application, but this relationship has not been adequately studied.

The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

INDICATIONS AND USAGE: Transdermal nitroglycerin is indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack.

CONTRAINDICATIONS: Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS: The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a nitroglycerin transdermal patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS: General: Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10 to 12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients had decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients: Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with light-headedness.

4

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Information for Patients: Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with light-headedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

See Patient Information at the end of this insert.

Drug Interactions: The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenesis studies with topically applied nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in *in vitro* cytogenetic tests in rat and dog tissues.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for 6 months prior to mating of the F₀ generation with treatment continuing through successive F₁ and F₂ generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F₀ generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

Pregnancy: Pregnancy Category C: Animal teratology studies have not been conducted with nitroglycerin transdermal systems. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be seen in the most commonly reported

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Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of light-headedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation.

of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great 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 nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see OVERDOSAGE).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Light-headedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE: Hemodynamic Effects: The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever, vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₅ reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2 to 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the

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Methemoglobinemia: Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₅ reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq 10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2 to 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial P_{O_2} . Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSE AND ADMINISTRATION: The suggested starting dose is between 0.2 mg/hr and 0.4 mg/hr. Doses between 0.4 mg/hr and 0.8 mg/hr have shown continued effectiveness for 10 to 12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10 to 12 hours is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12 to 14 hours and a daily patch-off period of 10 to 12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM: A patient leaflet is supplied with each carton.

HOW SUPPLIED: Nitroglycerin Transdermal System 0.1 mg/hr is a translucent rectangular patch with rounded corners (registered imprint 'Nitroglycerin 0.1 mg/hr' in white ink), affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal System 0.2 mg/hr is a translucent rectangular patch with rounded corners (registered imprint 'Nitroglycerin 0.2 mg/hr' in white ink), affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal System 0.4 mg/hr is a translucent rectangular patch with rounded corners (registered imprint 'Nitroglycerin 0.4 mg/hr' in white ink), affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal System 0.6 mg/hr is a translucent rectangular patch with rounded corners (registered imprint 'Nitroglycerin 0.6 mg/hr' in white ink), affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal Systems are available as follows:

Nitroglycerin Transdermal System Strength	Total Nitroglycerin in System	System Size	Carton Size	NDC Number
0.1 mg/hr	11.2 mg	4 cm ²	30 Systems	0378-9102-31
0.2 mg/hr	22.4 mg	8 cm ²	10 Systems	0378-9104-31
0.4 mg/hr	44.8 mg	16 cm ²	30 Systems	0378-9112-31
0.6 mg/hr	67.2 mg	24 cm ²	100 Systems	0378-9116-01

STORE AT ROOM TEMPERA-

glycerin 0.4 mg/hr in white ink, affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal System 0.4 mg/hr is a translucent rectangular patch with rounded corners (registered imprint "Nitroglycerin 0.4 mg/hr" in white ink), affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal System 0.6 mg/hr is a translucent rectangular patch with rounded corners (registered imprint "Nitroglycerin 0.6 mg/hr" in white ink), affixed to a clear, peelable liner, and is supplied in a foil-lined pouch.

Nitroglycerin Transdermal Systems are available as follows:

Nitroglycerin Transdermal System	Total Nitroglycerin in System	System Area	System Size	Carton Size	NDC Number
0.1 mg/hr	11.2 mg	4 cm ²	30 Systems	0378-9102-53	
0.2 mg/hr	22.4 mg	8 cm ²	30 Systems	0378-9102-53	
0.4 mg/hr	44.8 mg	16 cm ²	30 Systems	0378-9104-53	
0.6 mg/hr	67.2 mg	24 cm ²	30 Systems	0378-9112-53	
			100 Systems	0378-9118-53	

STORE AT ROOM TEMPERATURE 15° - 30°C (59° - 86°F). DO NOT REFRIGERATE.

Do not store outside of the protective package. Apply immediately upon removal from the protective package.

Keep this and all medication out of the reach of children.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED JULY 1997
NTG:RS

Patient Information

How to use NITROGLYCERIN TRANSDERMAL PATCH for the prevention of angina

The Nitroglycerin Transdermal Patch is easy to use - it has a clear peelable liner, and a special adhesive that keeps the patch firmly in place.

Where to place the Nitroglycerin Transdermal Patch

Select any area of skin on the body, EXCEPT the extremities below the knee or elbow. The chest is the preferred site. The area should be clean, dry, and hairless. If hair is likely to interfere with patch adhesion or removal, it can be clipped but not shaved. Take care to avoid areas with cuts or irritations. Do NOT apply the patch immediately after showering or bathing. It is best to wait until you are certain the skin is completely dry.

How to apply the Nitroglycerin Transdermal Patch

1. Each Nitroglycerin Transdermal Patch is individually sealed in a protective package. Open the pouch at the tear mark. Carefully remove the patch. The patch is printed with the wording "Nitroglycerin" and the amount of nitroglycerin delivered each hour. The patch is attached to a clear peelable liner. The liner has a slit which divides it into two strips. Hold the patch with the wording facing away from you. The slit should now be facing toward you. Rotate the patch as necessary to place the slit in an up and down position.



2. Bend both sides of the clear peelable liner away from you at the slit.



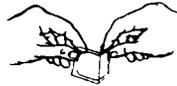
3. Slowly peel off only one of the strips of the clear liner. Do not touch the exposed sticky side of the patch.



4. Using the remaining strip as a "handle", apply the exposed sticky side of the patch to the skin. Press the sticky side on the chosen skin site and smooth down.



2. Bend both sides of the clear peelable liner away from you at the slit.



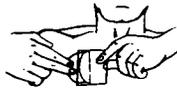
3. Slowly peel off only one of the strips of the clear liner. Do not touch the exposed sticky side of the patch.



4. Using the remaining strip as a "handle", apply the exposed sticky side of the patch to the skin. Press the sticky side on the chosen skin site and smooth down.



5. Fold back the unattached side of the patch. Grasp the remaining strip and remove it while applying the remainder of the patch to the skin. Press the patch on the skin and smooth down with the palm of your hand. Once the patch is in place, do not test the adhesion by pulling on it.



When Nitroglycerin Transdermal Patch is applied to your body, the nitroglycerin contained in the patch begins to flow from the adhesive surface through your skin at a uniform rate.

6. After applying the patch, wash hands to remove any drug.

7. At the time recommended by your doctor, remove and discard the patch.

8. Place a new patch on a different skin site (following steps 1 through 6) according to your doctor's instructions.

Please note:

Contact with water, as in bathing, swimming, or showering will not affect the patch. In the unlikely event that a patch falls off, discard it and put a new one on a different skin site.

Precautions:

The most common side effect is headache, which often decreases as therapy is continued, but may require treatment with a mild analgesic. Although uncommon, faintness, flushing, and dizziness may occur, especially when suddenly rising from the recumbent (lying horizontal) position. If these symptoms occur, remove the patch and notify your physician.

Skin irritation may occur. If it persists, consult your physician.

Keep these patches and all drugs out of the reach of children.

Important:

Your doctor may decide to increase or decrease the size of the patch, or prescribe a combination of patches, to suit your particular needs. The dose may vary depending on your individual response to the patch.

This patch is to be used for *preventing* angina, not for treating an acute attack.

STORE AT ROOM TEMPERATURE 15° - 30°C (59° - 86°F). DO NOT REFRIGERATE.

Do not store outside of the protective package. Apply immediately upon removal from the protective package.

MYLAN PHARMACEUTICALS INC.
Morgantown, WV 26505

REVISED JULY 1997
PL-NTG.R5

OFFICE OF GENERIC DRUGS
DIVISION OF CHEMISTRY II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 75-033

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS for ANDA SUBMISSION

Reference Drug: Transderm-Nitro[®]/Ciba Pharmaceuticals, Inc.
Patent and Exclusivity - None remaining, page 9.
Patent Certification - page 9.
Basis for Submission - page 7.

Note: The following patents are listed in the 'Orange Book' - 17th Edition: 4954344, 4849226, 4812313, all with expiration date of 12/4/2001.

5. SUPPLEMENT(s): N/A

PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Nitroglycerin Transdermal System
0.1 mg/hr.

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

12/20/96 - Original Submission
04/04/97 - Amendment
06/03/97 - Amendment
08/22/97 - Amendment **Subject of this review.**
10/02/97 - Amendment **Subject of this review.**

FDA:

02/28/97 - Acceptable for filing.
07/25/97 - First NA facsimile.

10. PHARMACOLOGICAL CATEGORY

Antiangina and coronary artery disease

11. Rx or OTC

R_x

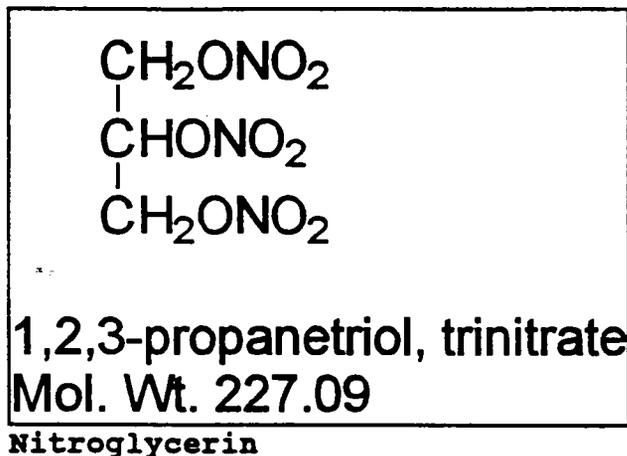
12. RELATED IND/NDA/DMF(s):

ANDA 75-033

Mylan/Nitroglycerin Patches

13. DOSAGE FORM 14. POTENCY
Transdermal Patch 0.1 mg/hr.

15. CHEMICAL NAME AND STRUCTURE



16. RECORDS AND REPORTS: N/A

17. COMMENTS

1. CMC is satisfactory.
2. Labels/Labeling are satisfactory.
3. BIO - review of A. Jackson is pending.
4. EER - acceptable, 6/4/97; but is needed for
5. MV - will not be requested since the methods were validated for ANDA 74-559 which is incorporated by reference in this ANDA.

18. CONCLUSIONS AND RECOMMENDATIONS:

Recommend Approval pending BIO review and EER for Lancaster Laboratories.

19. REVIEWER:
Robert C. Permisohn

DATE COMPLETED:

10/17/97

10/31/97

ANDA APPROVAL SUMMARY

ANDA NUMBER: 75-033

DRUG PRODUCT: Nitroglycerin Transdermal System

FIRM: Mylan Pharmaceuticals, Inc./Bertek, Inc.

DOSAGE FORM: Transdermal System STRENGTH: 0.1 mg/hr

CGMP STATEMENT/EER UPDATE STATUS: Acceptable 6/4/97; an update including is necessary.

BIO STUDY: Pending review by A. Jackson of the DOB.

METHODS VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Samples of the ds and this drug product were not tested at an FDA laboratory since validation of a companion product under ANDA 74-559 (incorporated in this application by reference) was conducted at WEAC. The procedures are acceptable for regulatory purposes in U.V. Venkataram Chemist's Review No. 4 for ANDA 74-559 dated 8/27/96. The methodology is the same as that validated under ANDA 74-559 in U.V. Venkataram Chemist's Review No. 1 for this ANDA dated 6/17/97. The firm has confirmed that all test methods for the ds, intermediate adhesive, intermediate laminate, and drug product are identical to those used in support of ANDA 74-559, with minor exceptions, in their amendment dated 8/22/97, for this ANDA. Also, validation data for the testing procedures can be found in this ANDA.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Container/closure: Yes; described below.

Description: A pouch formed by heat sealing two layers of pouching material with the patch between the layers. The pouching material consists of The pouches (in 30's and 100's) are boxed in cartons (not described).

Supplier: will supply preprinted packaging material with product name, potency, and name and address of patch manufacturer. DMF and LOA on page 657 of this ANDA.

Stability Protocol: Satisfactory

Stability Data: Satisfactory in support of the proposed expiration dating period of 24 mos. for the following lot:

<u>Lot#</u>	<u>Batch Size</u>	<u>Batch Record</u>	<u>Stability Conditions</u>
26C007E		Satisfactory	40°C/75% RH/3 months, 30°C/60% RH/12 months, 25°C/60% RH/12 months.

Batch size of "Intermediate Nitroglycerin Laminate" (lot # R&D-I313). Theoretical yield of "Nitroglycerin Transdermal System" doses (lot # 26C007E).

3 Actual yield of "Nitroglycerin Transdermal System" doses after the die

Mylan/Nitroglycerin Patches

- cutting step (lot # 26C007E).
- Actual yield of "Nitroglycerin Transdermal System" doses after the packaging step (lot # 26C007E).

LABELING:

FPL labels/labeling in the 8/22/97, amendment are satisfactory for approval per A. Vezza review dated 9/3/97, for this ANDA. Labeling is shared/common for companion ANDA 74-992, and both ANDA's should be approved at the same time as per "FOR THE RECORD" comment no. 4 in the C. Hoppes review dated 7/25/97, for this ANDA. The Reference Listed Drug for this ANDA and ANDA 74-992. This was brought to the attention of A. Vezza on 11/17/97 and he revised his review with deletion of comment 4. regarding codependence for approval of this ANDA and ANDA 74-992.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS O.K.):

Bio batch is the same as the stability batch. The ds is satisfactory per U.V. Venkataram review of DMF dated 5/25/97.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch is the same as the BIO batch. See "STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?" section above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The manufacturing process for the executed batch is the same as the proposed batch size. Comparison of the proposed production batch with the test batch is as follows:

<u>Parameter</u>	<u>Executed Batch</u>	<u>Production Batches</u>
Size		
Lot#		
Equipment		
Process Steps	Identified	Same as executed batch.
Process Parameters	Identified	Same as executed batch.
In-process Sampling	Identified	Same as executed batch.
In-process Tests & Specifications	Identified	Same as executed batch.

*Not identified in the proposed production record.

CHEMIST: Robert C. Permisohn

DATE: October 17, 1997. ^{10/31/97}

TEAM LEADER: Ubrani V. Venkataram, Ph.D.

DATE: October 27, 1997. ^{11/3/97}

2.1
1/20/84

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-033

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Nitroglycerin Transdermal System, 0.1 mg/hr

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of water, using USP Apparatus 5 (Paddle over disk) at 50 rpm. The test product should meet the following specifications:

- 1/2 hr NLT
- 1 hr NLT
- 2 hr NLT
- 4 hr NLT

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-033
ANDA DUPLICATE
DIVISION FILE
HFD-650/Division Sign Off
HFD-650/Jackson
BIO DRUG FILE
FIELD COPY

Review signed
11/20/97

X:\NEW\FIRMSAM\MYLAN\LTRS&REV\75033BIO.FDW

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY (STF)** Strengths: _____
Clinical: _____ Outcome: AC IC UN NC
Analytical: _____
2. **FOOD STUDY (STP)** Strengths: _____
Clinical: _____ Outcome: AC IC UN NC
Analytical: _____
3. **MULTIPLE DOSE STUDY (STM)** Strengths: _____
Clinical: _____ Outcome: AC IC UN NC
Analytical: _____
4. **DISSOLUTION DATA (DIS)** All Strengths
Outcome: AC IC UN NC
5. **STUDY AMENDMENT (STA)** Oct 2, 97 Strengths: 0.1 mg/h
Outcome: AC IC UN NC
6. **WAIVER (WAI)** Strengths: _____
Outcome: AC IC UN NC
7. **DISSOLUTION WAIVER (DIW)** Dec 20, 96 Submission
Strengths: 0.1 mg/h
Outcome: AC IC UN NC
8. **OTHER (OTH)** _____ Strengths: _____
Outcome: AC IC UN NC
9. **OTHER OPTIONS (less common):** Strengths: _____
a. Protocol (PRO) d. Special Dosage (STS)
b. Protocol Amendment (PRA) e. Study/Dissolution (STD)
c. Protocol/Dissolution (PRD) f. Bio study (STU)
Outcome: AC IC UN NC

OUTCOME DECISIONS:

AC - Acceptable
NC - No Action

UN - Unacceptable (fatal flaw)
IC - Incomplete

Nitroglycerin Transdermal Patch
ANDA # 75-033-0.1 mg/hr
Reviewer: Andre J. Jackson
WP# 75033WD.D96

Mylan Pharmaceuticals
Morgantown, West Va.
Submission Dated:
December 20, 1996
October 2, 1997

REVIEW OF A WAIVER REQUEST FOR NITROGLYCERIN TRANSDERMAL PATCH

Background

The firm is requesting a waiver for their manufacture of their 4cm² patch containing nitroglycerin with a release rate of 0.1 mg/hr. The product will be manufactured by Bertek Inc., 110 Lake Street, St. Albans, VT 05478. Bertek is a wholly owned subsidiary of Mylan Laboratories Inc.

The nitroglycerin patch which is the subject of this application has the same composition and manufacturing process as the Nitroglycerin Transdermal System contained in ANDA 74-559 which was approved in 1996. The only difference is in the die cutting process to obtain the correct size patch. Based on these similarities the human and animal studies designed to evaluate wearability and irritation potential of the nitroglycerin patch have not been repeated for this application. The original studies conducted and submitted in ANDA 74-559 are considered applicable to this application.

Table 1 . Comparative composition of 0.1 mg/hr patch and the approved 0.6 mg/hr patch.

<u>ACTIVE</u>	THEORETICAL	THEORETICAL
	mg/PATCH (4 cm²)	mg/PATCH (24 cm²)
Nitroglycerin	11.2 ¹	67.2 ¹
<u>INACTIVE</u>		

WhiteInk

Negligible

Negligible

¹ Nitroglycerin content is targeted at a constant 28 grams per square meter.

² Based upon targets of Nitroglycerin content and Non-volatile residue content in the
 ided for process loss to achieve a target potency of 28 grams of nitroglycerin per
 square meter (2.8 mg/cm²).

Dissolution

The dissolution study for nitroglycerin transdermal system was done as follows:

Apparatus: (5)-Paddle over disk, 50 RPM

Medium: 600 ml Water

No. of Units Analyzed: 12

Specifications:

(proposed) 1/2 hr NLT

1 hr NLT

2 hr NLT

4 hr NLT

Assay:

The results are presented in Table 2.

Comments:

1. The firm submitted a letter to the Division of Bioequivalence dated October 2, 1997 accepting the dissolution specification of NLT \geq 4 hr.
2. The 0.1 mg/hr formulation is compositionally proportional to the 0.6 mg/hr formulation.
3. The reference product did not exhibit dissolution for 2 hours.

Recommendation:

1. The dissolution testing conducted by Mylan Pharmaceutical on its transdermal nitroglycerin patches, Lot No. 26C007E, 0.1 mg/hr comparing it to Summit Pharmaceuticals Transderm-Nitro^R patch 0.1 mg/hr is acceptable. The firm has conducted an acceptable in-vivo bioequivalence study, January 6, 1995 comparing its 0.6 mg/hr transdermal patch of the test product with the 0.6 mg/hr transdermal patch of the reference product Transderm-Nitro^R Manufactured by Summit Pharmaceuticals. The formulation for the 0.1 mg/hr strengths is proportionally similar to the 0.6 mg/hr strength of the test product which underwent bioequivalency testing. The waiver of in-vivo bioequivalence study requirements for the 0.1 mg/hr transdermal patch for the test product is granted. The 0.1 mg/hr transdermal patch of the test product are therefore deemed bioequivalent to the 0.1 mg/hr transdermal patches of Transderm-Nitro^R manufactured by Summit Pharmaceuticals.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using apparatus (5)-Paddle over disk at 50 RPM in 600 ml water. The test product should meet the following specifications:

- 1/2 hr NLT
- 1 hr NLT
- 2 hr NLT
- 4 hr NLT

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

Concur:

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 10/28/97

Date: 10/20/97

ANDA# 75033 (original, duplicate) HFD-600 (Hare), HFD-630, HFD 652 (Huang, Jackson), Drug File, Division File, HFD-650 (Division Director)

Table 2 . In Vitro Dissolution Testing

Drug (Generic Name): Nitroglycerin Transdermal System
 Dose Strength: 0.1 mg/hr
 ANDA No.: 75-033
 Firm: Bertek Pharmaceutical
 Submission Date: December 20, 1996
 File Name: 75033DW.D96

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: USP modified paddle over disk(5)
 RPM: 50
 No. Units Tested: 12
 Medium: Water
 Volume: 600 ml
 Specifications:
 (proposed) 1/2 hr NLT
 1 hr NLT
 2 hr NLT
 4 hr NLT

*DBE recommends
 NLT ... at 4hr. YHM*

Reference Drug: Transderm-Nitro^x
 Assay Methodology:

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 26C007E Strength(mg) 0.1 mg/hr			Reference Product Lot # C1530 Strength(mg) 0.1 mg/hr		
	Mean %	Range	%CV	Mean %	Range	%CV
30	62.0		1.4	0		
60	79.0		1.6	0		
120	92.0		1.4	8		32
240	98.0		1.4	14		8.2



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

OCT 2 1997

TOA ORIG AMENDMENT
FA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

RE: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.1 mg/hr
ANDA #75-033
Response to September 11, 1997 Telephone Call

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above and to a September 11, 1997, telephone call regarding this application which was received from the Division of Bioequivalence.

In response to the discussions of September 11, 1997, this amendment provides for a revision to the dissolution specifications used for the release and stability of Nitroglycerin Transdermal System, 0.1mg/hr. As requested by the Agency the dissolution limit for the 4-hour timepoint has been changed from Not Less Than to Not Less Than. This is consistent with the specifications for the other three approved strengths of the Nitroglycerin Transdermal System product (0.6mg/hr, 0.4mg/hr, and 0.2mg/hr). All other finished product specifications remain as previously submitted. Enclosed, in Attachment A, are revised finished product specifications which provide for the noted change. Attachment B contains an updated post-approval stability protocol which has been revised to include the new dissolution limit.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic drugs, has been forwarded to the FDA's Boston District Office.

This amendment is submitted in duplicate. Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

RECEIVED

OCT 03 1997

GENERIC DRUGS

Department—enclosures
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Business Development
Human Resources

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(304) 599-7284
(304) 599-7284
(304) 598-5406

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Label Control
Legal Services
Maintenance & Engineering
Medical Unit

(304) 285-6404
(800) 848-0463
(304) 598-5408
(304) 598-5411
(304) 598-5445

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Quality Control
Research & Development
Sales & Marketing

(304) 598-5401
(304) 598-5407
(304) 285-6409
(304) 598-3232

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S. (304) 599-2595

AUG 22 1997

*Labeling satisfactory for
approval - review by staff
9/3/97 a Vjgga
N / FA*

AUG 25 1997

GENERIC DRUGS

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

RE: NITROGLYCERIN TRANSDERMAL SYSTEM, 0.1 mg/hr
ANDA #75-033
Response to Agency Correspondence Dated July 25, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's comments submitted via facsimile on July 25, 1997. Mylan wishes to amend this application with the following:

REGARDING CHEMISTRY ISSUES:

FDA COMMENT 1: Please include in the components statement all components of

MYLAN RESPONSE: Due to the proprietary nature of the compositional information, all four components listed in the Agency's comment are covered by Drug Master Files (DMFs). Letters of Authorization giving the FDA permission to refer to these DMFs on behalf of Mylan were provided in Section VIII of the original application. However, to comply with the Agency's comment, information on the composition of the four components was requested from each of the respective suppliers by Bertek Inc. Bertek manufactures the finished product for Mylan. Qualitative compositions for

received from the suppliers and the documentation obtained is provided in Attachment 1. would not provide Mylan with the qualitative composition for and a letter indicating this is also provided in Attachment 1.

For proprietary reasons no quantitative information was made available to Mylan. Based on the information obtained, revised qualitative composition statements for the and Intermediate Nitroglycerin Coated Laminate, 28 g/m² / Nitroglycerin Transdermal System, 0.1 mg/hr are provided in Attachment 1. Please refer to the associated DMFs should additional information be required pertaining to the composition or manufacturing instructions for the components.

Department—Fax Numbers

Accounting (304) 285-6403
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FDA COMMENT 2: Please submit cGMP certification from Bertek Inc./Medical Products Division and

MYLAN RESPONSE: Letters of cGMP certification from Bertek Inc., Medical Products Division and are attached (see Attachment 2).

FDA COMMENT 3: The Product Out-Date sheet suggests that the production may be extended up to 3 months from coating to die cutting. We recommend that the production be completed in a more timely manner or stability data should be provided in support of this plan.

MYLAN RESPONSE: Three month stability data for the Nitroglycerin Intermediate Laminate, 28 g/m² is attached (see Attachment 3). Please note that each rotation represents a layer of material on the outside of the roll - the first rotation is always discarded prior to continuing the manufacturing process.

FDA COMMENT 4: The production record does not specify the slitting, die cutting, printing, and pouching machinery. Are they the same as those used in the executed batch? Please submit revised batch records identifying these equipment.

MYLAN RESPONSE: Each Batch Production Record has spaces (labeled, "Machine Number ____") which allows the operator to identify the piece of equipment used at each stage in the manufacturing process. The executed Batch Production Records are not approved without that information. The equipment used for manufacture of the exhibit lot is the same as that which would be used for future commercial lots.

FDA COMMENT 5: Please submit available controlled room temperature data to date.

MYLAN RESPONSE: Updated stability summary tables for Nitroglycerin Transdermal System, 0.1 mg/hr are attached (see Attachment 4). These data provide stability results through 12 months of storage. These data continue to support the proposed 24 month expiration dating period.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

FDA COMMENT 1: Please confirm that the analytical methods for drug substance and drug product are the same as those used in ANDA 74-559. We note that ANDA 74-559 has been incorporated in this application by reference.

MYLAN RESPONSE: All test methods used for the drug substance, intermediate adhesive, intermediate laminate and drug product are identical to those used in support of ANDA 74-559, (Nitroglycerin Transdermal System, 0.6 mg/hr) with the following exceptions:

- a) **DRUG SUBSTANCE:** The assay and related compounds methods for the drug substance were revised to allow for use of a suitable reference standard other than USP. The identification method for the drug substance was not revised but refers directly to the assay method and therefore was indirectly updated as well. (USP Nitroglycerin reference standard has been unavailable for extended periods of time.)
- b) **INTERMEDIATE ADHESIVE BLEND:** No differences.
- c) **INTERMEDIATE LAMINATE:** The content uniformity method for the intermediate laminate was revised to allow for use of a suitable reference standard other than USP. (USP Nitroglycerin reference standard has been unavailable for extended periods of time.)
- d) **DRUG PRODUCT:** The assay, uniformity, dissolution and chromatographic purity methods for the drug substance were revised to allow for use of a suitable reference standard other than USP. (USP Nitroglycerin reference standard has been unavailable for extended periods of time.)
- e) **DRUG PRODUCT:** A method for analysis of monomers was added to the Nitroglycerin Transdermal System, 0.1 mg/hr application that was not originally submitted for the Nitroglycerin Transdermal System, 0.6 mg/hr.
- f) **DRUG PRODUCT:** Microbial testing for the Nitroglycerin Transdermal System, 0.6 mg/hr product was changed from a swab method performed by Mylan Laboratories to an immersion method performed by (ANDA 74-559/S-001, Approved July 30, 1997). Microbial testing for the Nitroglycerin Transdermal System, 0.1 mg/hr product uses the immersion method performed by

FDA COMMENT 2: Please note that your dissolution test, method and specifications will be reviewed by our Divisions of Bioequivalence. We may request revisions to your release and stability specifications based on their recommendations.

MYLAN RESPONSE: Mylan acknowledges that the dissolution test, method and specifications for the Nitroglycerin Transdermal System, 0.1mg/hr product will be reviewed by the Division of Bioequivalence and that revisions to our release and stability specifications may be requested based on the Division's recommendations.

REGARDING LABELING ISSUES:

MYLAN RESPONSE: Attachment 10 contains twelve (12) copies of the following final printed patient package inserts and professional package insert for Nitroglycerin Transdermal System, 0.1mg/hr. Attachment 9 contains twelve (12) copies of color printer's proof labeling for the pouch and cartons (six copies in the

archival copy and six copies in the review copy). Attachment 8 contains twelve (12) copies of the draft labeling for the patch.

The enclosed labeling incorporates the revisions requested in the Agency's letter of July 25, 1997. For the convenience of the reviewer, Mylan responses to this letter in regard to labeling are provided in Attachment 6.

In order to facilitate the review of this labeling, Attachment 7 contains a side-by-side comparison of the labeling to that which was previously submitted. It is noted that prior to approval of this application, the Agency reserves the right to request further changes in the Mylan labeling based upon changes in the approved labeling of the listed drug or upon further review of the application.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment as submitted to the Office of Generic drugs has been forwarded to the FDA's Boston District Office.

For your reference, a copy of the Agency letter Dated July 25, 1997, is enclosed in Attachment 5.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6507.

Sincerely,



Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

JUL 25 1997

NDA 75-033
Mylan/Nitroglycerin Patches

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-033 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Nitroglycerin Delivery System, 0.1 mg/hr.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Please include in the components statement all components of _____
2. Please submit cGMP certification from Bertek Inc./Medical Products Division and
3. The Product Out-Date sheet suggests that the production may extend up to 3 months from coating to die cutting. We recommend that the production be completed in a more timely manner or stability data should be provided in support of this plan.
4. The production record does not specify the slitting, die cutting and pouching machinery. Are they the same as the those used in executed batch? Please submit revised batch records identifying the equipment.
5. Please submit available controlled room temperature data to date.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please confirm that the analytical methods for drug substance and drug product are the same as those used in ANDA 74-559. We note that ANDA 74-559 has been incorporated in this application by reference.



NDA 75-033

Mylan/Nitroglycerin Patches

2. Please note that your dissolution test, method and specifications will be reviewed by our Division of Bioequivalence. We may request revisions to your release and stability specifications based on their recommendations.

Sincerely yours,

10 1
Lr1

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 4, 1997

NAT
4/10/97
NEW CORRESP
NC

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: NITROGLYCERIN TRANSDERMAL SYSTEM,
0.1 MG/HR
ANDA NO: 75-033

Dear Mr. Sporn:

Mylan hereby amends this application with the attached "Paragraph IV" certification and the following certification of notice to each owner of the patents and the holder of the approved application.

Pursuant to Section 505(j)(2)(B)(i) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, concurrently with the filing of this amendment, provided notice to each owner of the patents which are the subject of the certification, or their representatives, and also to the holder of the approved application for the listed drug claimed by said patents. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

Further, Mylan commits to amend this application pursuant to 21 CFR 314.95(e) to provide certification that notifications sent to the patent owners and application holder have been received.

Sincerely,

Dawn Beto
Dawn J. Beto, Esq.
Senior Counsel

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APR 07 1997

GENERIC DRUGS

Nadine
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DJB/dc

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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

April 4, 1997

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: NITROGLYCERIN TRANSDERMAL SYSTEM,
0.1 MG/HR
PATENT NOs: 4,954,344, 4,849,226 and 4,812,313
PARAGRAPH IV CERTIFICATION
ANDA NO: 75-033

Dear Mr. Sporn:

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patents 4,954,344, 4,849,226 and 4,812,313 are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Nitroglycerin Transdermal System, 0.1 mg/hr for which this application is submitted.

Mylan further certifies that according to the exclusivity information published by the FDA in that document entitled "Approved Drug Products with Therapeutic Equivalence" 16th Edition and the twelfth Supplement thereto, the referenced product is not covered by any exclusivity.

Mylan will market its Nitroglycerin Transdermal System upon approval of this application and resolution of the validity, enforcement, or infringement of patent numbers 4,954,344, 4,849,226, and 4,812,313.

Sincerely,

Dawn J. Beto, Esq.
Senior Counsel

DJB/dc

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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 3, 1997

NC

Offices of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: NITROGLYCERIN TRANSDERMAL SYSTEM,
0.1MG/HR
ANDA NO. 75-033

Dear Mr. Sporn:

Pursuant to 21 CFR 314.95(e), Mylan hereby amends the above referenced application with documentation of receipt of the notice required by 21 CFR 314.95(a). I have enclosed documentation of receipt by the owners of the patent, and the holder of the application for the listed drug claimed by said patent. Proof of delivery by Certified Mail, Return Receipt evidences receipt by Novartis Pharmaceuticals Corp. on April 7, 1997, and by Alza Corporation on April 9, 1997.

Sincerely,

Dawn J. Beto, Esq.
Senior Counsel

DJB/dc

Enclosures

**RECEIVED
JUN 05 1997
GENERIC DRUGS**

Handwritten: Madeline 6/10/97

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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

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2/14/97
Auremarie H. Weibel

DEC 20 1996

2/14/97
YH

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Nitroglycerin Transdermal System, 0.1 mg/hr

Dear Mr. Sporn,

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94 we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Nitroglycerin Transdermal System, 0.1 mg/hr

This application consists of a total of 9 volumes:

- Archival Copy - 3 volumes.
- Review Copy - 4 volumes.
 - Technical Section For Chemistry - 3 volumes.
 - Technical Section For Pharmacokinetics - 1 volume.
- Analytical Methods - 2 extra copies, 1 volume each.

RECEIVED

DEC 23 1996

GENERIC DRUGS

This application provides for the manufacture of patches (4 cm²) containing nitroglycerin with a release rate of 0.1 mg per hour. The product will be manufactured for Mylan Pharmaceuticals Inc. by Bertek Inc., 110 Lake Street, St. Albans, VT 05478. Bertek is a wholly owned subsidiary of Mylan Laboratories Inc.

The nitroglycerin patch which is the subject of this application represents a new dosage strength (line extension) of the following approved Nitroglycerin Transdermal System products: 0.6 mg/hr (ANDA 74-559), 0.4 mg/hr (ANDA 74-607), and 0.2 mg/hr (ANDA 74-609). The new 0.1 mg/hr product has the same composition and manufacturing process as that approved for the other 3 strengths. The only difference is in the die cutting process to obtain the correct size patch. Based on these similarities the human and animal studies designed to evaluate wearability and irritation potential of the nitroglycerin patch have not been repeated for this application. The original studies conducted and submitted in ANDA 74-559 are considered applicable to this application and are therefore incorporated by reference as noted in Section XXI.

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Douglas L. Sporn
Page 2 of 2

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Boston District Office.

For more detailed information regarding the organization of this ANDA, please refer to the Introduction, Reader's Guide and Master Table of Contents following this letter.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road P.O. Box 4310, Morgantown, WV 26504-4310 [FAX No. (304) 285-6407, Phone No. (304) 599-2595, ext. 6600].

Sincerely,



Frank R. Sisto
Executive Director
Regulatory Affairs