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April 17, 2003

Via Hand Delivery

2094 '03 APR 17 P4:43

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Citizen Petition to Establish Appropriate Approval Standards for Generic Clonidine Transdermal Products
Docket No.: 01P-0470/CP 1

Dear Sir or Madam:

We represent Mylan Technologies, Inc. ("Mylan"), holder of a pending application for a generic clonidine transdermal product. Pursuant to 21 C.F.R. §10.30(d), Mylan submits these additional comments in opposition to the above-referenced Citizen Petition to Establish Appropriate Approval Standards for Generic Clonidine Transdermal Products (the "Citizen Petition"), filed by Arnold and Porter on behalf of Boehringer Ingelheim Pharmaceuticals, Inc. ("BI") on October 10, 2001. Mylan previously submitted comments in opposition to the Citizen Petition on April 9, 2002, in which Mylan provided reasons why the bioequivalency testing proposed by BI is unnecessary. BI also submitted a supplement to the Citizen Petition on February 20, 2002 (of which Mylan was unaware when filing its opposition on April 9), and a

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response to Mylan's comments on September 4, 2002.[1] BI also submitted to FDA on March 3, 2003 a meeting request and proposed agenda.

Mylan has an interest in the outcome of the Citizen Petition because the petitioner has requested, inter alia, that the FDA not approve any new or pending ANDA for a generic clonidine transdermal product that has a controlled release mechanism or inactive ingredients that differ from BI's own clonidine transdermal product (Catapres-TTS), unless a showing is made that the proposed generic product is safe and effective, and meets new bioequivalence standards proposed by BI.[2]

The crux of BI's arguments is that Mylan be required to show that Mylan's Clonidine Transdermal System ("Mylan CTS") does not pose a risk to persons who, according to BI, possess highly permeable skin. However, BI does not define what it means by "persons with highly permeable skin." BI also fails to provide evidence or data showing that Catapres TTS effectively controls release rate on these persons with such so-called "highly permeable skin." BI's request for new requirements to address what is nothing more than normal variability in skin permeability will only have the effect of keeping generic clonidine products off the market. While BI protests that its petition is motivated by safety and efficacy rather than competitive concerns, its arguments are suspect in view of its failure (i) to provide any definition or criteria defining "a person with highly permeable skin," (ii) any evidence that such persons exist, or (iii) any evidence that its own Catapres TTS product provides any enhancement of safety or efficacy in such persons.

Mylan respectfully submits that no additional requirements are necessary for approval of Mylan CTS, and that the BI Citizen Petition should be denied for the following additional reasons. First, transdermal delivery systems based on a drug-in-adhesive release rate control

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[1] In BI's September 4, 2002 response, BI asserted on page 2 that Mylan has not responded to the scientific data and expert opinion provided by BI in the Supplement. The present response is supported by the Declaration by Dr. Jonathan Hadgraft, a leading scientific expert in the field of skin permeation and transdermal drug delivery. In his Declaration (attached as Exhibit B), Dr. Hadgraft rebuts the testimony of BI's experts, Drs. Hopfenberg and Maibach, and explains that the "rate control" membrane in Catapres TTS is really not rate controlling, as BI asserts. Arnold & Porter's arguments concerning the so-called rate-controlling membrane are the principal bases of BI's Citizen Petition.

[2] In the February 20, 2002 Supplement, BI expanded its initial request in the Citizen Petition for additional bioequivalence testing, asking FDA not to approve under an ANDA a clonidine patch not containing a rate-controlling membrane, irrespective of whether the patch satisfied the bioequivalence testing suggested by BI in the Citizen Petition.

mechanism, like Mylan CTS, have previously been approved as generic equivalents of NDA-approved transdermal systems containing so-called rate-controlling membranes. Second, FDA has approved, under both NDA's and ANDA's, many transdermal delivery systems that are based on a drug-in-adhesive release rate control mechanism, and those systems have been shown to be safe and effective. Third, FDA has determined in at least one instance that the same mechanism of rate control is not required for a generic equivalent of an NDA-approved extended release product. Fourth, the delivery mechanisms of Mylan CTS and Catapres TTS are substantially the same. Fifth, the so-called rate-controlling membrane in Catapres TTS does not control delivery rate of clonidine. Sixth, adhesive cold flow is not an issue with Mylan CTS. Seventh, a drug content within 10% of the NDA-approved transdermal system is not required. Eighth, Mylan CTS has no greater potential for sensitization than Catapres TTS.

A. Transdermal Delivery Systems Based on a Drug-in-Adhesive Release Rate Control Mechanism Have Been Approved as Generics to NDA-Approved Transdermal Systems Containing So-Called Rate Controlling Membranes

On page 6 of the Citizen Petition, BI argues that "FDA has stated, patches '*have to have the same controlled release mechanism, or they are not going to be considered as pharmaceutically equivalent.*" (emphasis in the original) However, at least one transdermal delivery system based on a drug-in-adhesive release rate control mechanism, like Mylan CTS, has been approved as a generic to NDA-approved transdermal systems containing a rate-controlling membrane. The FDA approved Mylan's drug-in-adhesive nitroglycerin transdermal system as AB rated to Ciba-Geigy's TransdermNitro, which is said to contain a rate-controlling membrane.

There is also at least one example of a drug-in-adhesive transdermal system approved as a generic to an NDA-approved system that was based on a release mechanism other than a drug-in-adhesive mechanism. In 1997, Sano obtained approval for a generic equivalent to the Habitrol nicotine patch (ANDA 74-645, 74-611, and 74-612). Habitrol contains a non-woven pad containing nicotine in solution, which pad is sandwiched between two adhesive layers. The system also contains a backing layer and release liner. Sano's generic product is a drug-in-adhesive system, consisting of a drug-in-adhesive layer between a backing layer and a release liner.

B. Transdermal Delivery Systems Based on a Drug-in-Adhesive Release Rate Control Mechanism Have Been Shown to be Safe and Effective

Transdermal delivery systems initially were based on the premise that the skin does not provide an adequate barrier to transdermal delivery and that a rate-controlling membrane was required to control the rate of drug absorption. Subsequent investigation, however, has shown

that membrane control is neither effective nor required.

FDA has approved many transdermal delivery systems based on a drug-in-adhesive release rate control mechanism, under both NDA's and ANDA's, because these systems have been shown to be safe and effective. FDA-approved transdermal systems that use a drug-in-adhesive release rate control mechanism include those delivering nitroglycerin, nicotine, oxybutynin, estradiol and other hormones. Examples of approved transdermal systems that use the drug-in-adhesive design are:

Product	Generic Name	NDA#	Company Name
NitroDur	Nitroglycerin film, extended release, transdermal	20-145	Key Pharmaceuticals
Vivelle	Estradiol film, extended release, transdermal	20-323	Novartis
Vivelle-Dot	Estradiol film, extended release, transdermal	20-538	Novartis
Climara	Estradiol film, extended release, transdermal	20-375	Berlex Labs
Evra	Ethynyl Estradiol, Norelgestromin film, extended release, transdermal	21-180	Ortho-McNeil Pharmaceutical
Nicoderm CQ	Nicotine film, extended release, transdermal	20-165	Aventis Pharmaceuticals
Nicotrol	Nicotine film, extended release, transdermal	20-536	Pharmacia and Upjohn
Oxytrol	Oxybutynin film, extended release, transdermal	21-351	Watson Labs
Combipatch	Estradiol, Norethindrone Acetate, film, extended release, transdermal	20-870	Novartis

Reference Listed Drug	Generic Name	ANDA #	Sponsor
NitroDur	Nitroglycerin film, extended release, transdermal 0.1mg/hr	75-076	Mylan
NitroDur	Nitroglycerin film, extended release, transdermal 0.2mg/hr	75-073	Mylan
NitroDur	Nitroglycerin film, extended release, transdermal 0.4mg/hr	75-075	Mylan
NitroDur	Nitroglycerin film, extended release, transdermal 0.6mg/hr	74-992	Mylan
NitroDur	Nitroglycerin film, extended release, transdermal 0.1mg/hr	89-771	3M
NitroDur	Nitroglycerin film, extended release, transdermal 0.2mg/hr	89-772	3M
NitroDur	Nitroglycerin film, extended release, transdermal 0.4mg/hr	89-773	3M
NitroDur	Nitroglycerin film, extended release, transdermal 0.6mg/hr	89-774	3M
TransdermNitro	Nitroglycerin film, extended release, transdermal 0.1mg/hr	75-033	Mylan
TransdermNitro	Nitroglycerin film, extended release, transdermal 0.2mg/hr	74-609	Mylan
TransdermNitro	Nitroglycerin film, extended release, transdermal 0.4mg/hr	74-607	Mylan
TransdermNitro	Nitroglycerin film, extended release, transdermal 0.6mg/hr	74-559	Mylan

Climara	Estradiol film, extended release, transdermal 0.05mg/day	75-233	Mylan
Climara	Estradiol film, extended release, transdermal 0.1mg/day	75-182	Mylan
Habitrol	Nicotine film, extended release, transdermal 7 mg/24 hrs	74-645	Sano
Habitrol	Nicotine film, extended release, transdermal 14 mg/24 hrs	74-611	Sano
Habitrol	Nicotine film, extended release, transdermal 21 mg/24 hrs	74-612	Sano

Thus, based on FDA policy, a drug-in-adhesive mechanism is an appropriate release rate control mechanism for a generic clonidine transdermal system.

C. FDA Has Determined That the Same Mechanism of Rate Control Is Not Required for NDA-Approved and Generic Products

The FDA has rejected arguments similar to those presented by BI in connection with oral sustained release products. In particular, the agency has determined that the same mechanism of rate control is not required for an NDA-approved product and the generic version of that product. FDA's position has been that therapeutic equivalence between the reference drug and its generic counterpart requires only compliance with the current bioequivalency standards for rate and extent of drug absorption.

For example, Pfizer argued unsuccessfully that generic versions of Procardia XL must incorporate the same rate-controlling mechanism -- the so-called OROS technology. FDA concluded that a generic product employing an erodible matrix did not constitute a new dosage form, as Pfizer had argued. FDA ruled that imposing a restriction that the generic and NDA-approved products have the same rate control mechanism was unnecessary, as long as bioequivalency was established. A copy of the court's decision upholding the FDA's position is attached as Exh. A.

D. The Delivery Mechanisms in Catapres TTS and Mylan TTS Are Substantially the Same

BI's arguments are based on the assumption that all monolithic patches depend for rate control on the skin alone. For example, BI's expert, Dr. Hopfenberg, asserts (in ¶¶ 11-12) with respect to monolithic patches: "[I]f the skin itself did not present an effective barrier that plays a significant role in limiting drug delivery, the drug would be released at a rate that would be extremely high initially, would subsequently decrease monotonically with time, and would never achieve a steady-state rate." However, Dr. Hopfenberg's conclusion is not correct for Mylan CTS, which, although a "monolithic" patch, contributes essentially the same amount of control to the delivery rate of clonidine as does Catapres TTS. The Mylan CTS and Catapres TTS products have substantially the same mechanisms for delivering steady state plasma levels of clonidine. As with Catapres TTS, Mylan CTS contains a reservoir of undissolved clonidine in a polyisobutylene (PIB) and mineral oil (MO) adhesive matrix that replenishes solubilized clonidine at the skin surface of the matrix, thereby maintaining a steady and controlled release of clonidine to skin. The release rate of clonidine is controlled by the concentration of solubilized

clonidine at the skin surface, which in turn is controlled by the dissolution rate of undissolved clonidine maintained in a saturated solution of clonidine within the PIB/MO matrix. The dissolved drug then diffuses to and through the skin. Because the driving force for diffusion remains constant over the 7-day use of the product, steady state plasma levels are reliably achieved. Also relevant is that Mylan CTS delivers clonidine at half the amount per unit area as compared to Catapres TTS, and therefore has almost twice the surface area of Catapres TTS, with equal biodelivery. See Declaration of Jonathan Hadgraft, D.Sc. ("Hadgraft Decl."), ¶¶ 10-11 (Exh. B) This difference in the rate of delivery is further evidence that rate control is inherent in the Mylan CTS product.

E. The Membrane in Catapres TTS Is Not Rate Limiting

BI argues that because clonidine is a narrow therapeutic index (NTI) drug,[3] and because skin can have varying degrees of permeability from site to site and patient to patient, a rate-controlling membrane is required in a clonidine transdermal delivery system to insure patient safety from excessive systemic clonidine levels. BI characterizes a clonidine transdermal patch that lacks a rate-controlling membrane as "a radical departure" from Catapres TTS. February 20, 2002 Supplement, at 1. BI is mistaken.

First, variability in skin permeability is normal and is not unique to clonidine. It varies from subject to subject, as does oral absorption of the active component from oral controlled release formulations. As BI's experts admit, the variability in skin permeability from site-to-site in the body and subject-to-subject has been well known and well documented for more than twenty years. Nitroglycerin, estradiol, nicotine, and testosterone all exhibit this variability. Clonidine is not an exception. Indeed, site-to-site and subject-to-subject variability in clonidine absorption is exhibited by Catapres TTS.[4] Furthermore, BI has failed to offer any definition of persons with high skin permeability relative to those persons having normal variability in skin permeability, or indeed that such persons even exist.

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[3] While clonidine has been characterized as an NTI drug, the FDA-approved package insert indicates for oral Catapres therapy that "[m]ost adverse effects are mild and tend to diminish with continued therapy." (Exh. C)

[4] See Hopkins et al., "Absorption of clonidine from a transdermal therapeutic system when applied to different body sites," in Mild Hypertension - Current controversies and new approaches, MA Weber and CJ Mathias (Eds) (1985) (showing intra-site variability) (Exh. D); S. Toon, "Phase I Pharmacokinetic Assessment of the Clonidine Transdermal Therapeutic System," Eur. J. Pharm. Biopharm., 41(3) 184-88 (1995) (showing intra-subject and inter-subject variability) (Exh. E).

Second, the so-called rate-controlling membrane in Catapres TTS does not control the delivery rate of clonidine, which rate is controlled instead by both the transdermal system and the skin. Indeed, there is a substantial amount of evidence that the membrane in Catapres TTS does not control the rate of clonidine delivery. This evidence includes the following:

1. Under Maximum Release Conditions, Mylan CTS and Catapres TTS Deliver the Same Amounts of Clonidine

In vitro drug release testing simulates the maximum possible release of drug (because the patches are in direct contact with the aqueous sink), and thus represents a "worst case scenario" for risk assessment and determining the degree of rate control provided by Mylan CTS. Mylan's ANDA includes results of such *in vitro* drug release testing and compares the release of clonidine from Catapres TTS and Mylan CTS over 7 days into aqueous media at pH 3.2.[5] Those results and data (summarized in Exh. F) show that Mylan CTS releases the same or even lower amounts of drug as Catapres TTS. The *in vitro* assay into aqueous media is the best way to determine any differences in rate control between the two systems, because the aqueous media, unlike skin, presents no barrier to permeation of the drug. (Hadgraft Decl., ¶ 12 (Exh. B))

2. Clinical Testing Shows that the Membrane in Catapres TTS Is Not Rate Limiting

Clinical testing establishes that the rate control membrane in Catapres TTS does not control the rate of clonidine delivery.

i. In one study conducted by Toon et al.,[6] a group of twelve healthy subjects was treated with a 3.5 cm^2 Catapres TTS patch containing 2.5 mg of clonidine base. The average rate of clonidine absorption in vivo (4.32 μg/h) from Catapres TTS was much lower than the observed in vitro rate of release of clonidine (11.6 μg/h) (see Table 1).[7] It was concluded that this difference could be due to the skin's being "a significant rate-limiting step" in the release of clonidine from the Catapres TTS system. Id. at 21.

The study results also highlighted one of the subjects (subject 6), whose cumulative rate

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[5] Importantly, *in vitro* drug release into an acidified water receptor solution also was used by Enscore et al. (Exhibit S to BI's February 20, 2002 Supplement to Citizen Petition) to simulate the upper limit of drug release potential from the Catapres TTS system.

[6] J. Pharm. Pharmacol., 1989, 41:17-21 (Exh. G).

[7] Toon et al. note beneath Table 1 that the in vitro release data were supplied by BI.

of absorption of clonidine was much higher than that of the other eleven group members (8.1 μg/h vs. 2 μg/h). This difference was ascribed to the subject's having exercised.[8] Importantly, this is the type of enhanced delivery that BI's expert, Dr. Maibach, declared would be prevented by the so-called rate-controlling membrane in Catapres TTS.[9]

Toon et al.'s results also are important in that they show the greater extent of drug absorption in subject 6 for the first 48 hours, as compared to the other subjects. As shown in Figure 3, subject 6 absorbed 60% of the total dose by 48 hours, with the remaining 40 % of the dose being absorbed over the remaining 5 days of patch wear. As explained by Dr. Hadgraft, the enhanced dose absorbed by subject 6 for the first 48 hours was 400% greater than the labeled dose for the first 48 hours for Catapres TTS. (Hadgraft Decl., ¶ 14 (Exh. B)) Also important, as shown in Figure 3, was that the delivery rate for Catapres TTS in subject 6 decreased over days 4-7, thus showing that Catapres TTS did not deliver clonidine to this subject at a constant rate over the 7 day period. Pursuant to Dr. Maibach's rationale, these results should have occurred with a generic patch not containing a rate control membrane, but not with Catapres TTS:

> "For a patient with high skin permeability, the rate-limiting barrier in the Catapres-TTS will be essential to controlling the rate at which the drug goes from the patch to the systemic circulation. In those individuals, a generic patch that does not have the rate-limiting barrier will potentially send high levels of clonidine into the body during the early period of application, with correspondingly lower levels at later times."

Maibach Decl., ¶ 7.

ii. In another study, Hopkins et al.[10] investigated in a group of twelve healthy subjects

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[8] The authors concluded that subject 6's increased rate of clonidine absorption may have reflected "an increased perfusion of the musculature underlying the site of application." Id. at 21.

[9] Dr. Maibach states in ¶ 8 of his Declaration that "the potential that exercise could increase absorption of drug from a transdermal patch" due to the increased rate of blood flow making "the skin appear temporarily more permeable than would otherwise be the case." Dr. Maibach concludes: "It is thus reasonable to expect that an increase in absorption, in the absence of a rate-limiting barrier within the patch, could be anticipated in at least some persons in instances of exercise."

[10] Hopkins et al., "Absorption of clonidine from a transdermal therapeutic system when applied to different body sites," in Mild Hypertension - Current controversies and new approaches, MA Weber and CJ Mathias (Eds) (1985) (Exh. D).

whether the release of clonidine is affected by the site of application of Catapres TTS. The sites chosen for investigation were the upper arm, the upper outer thigh, and the chest. Figure 2 shows that in one subject (subject 4), the plasma clonidine concentration was highest following application of Catapres TTS to the chest and lowest when applied to the upper outer thigh. Figure 3 shows the mean plasma concentrations for the group, again showing noticeable site-to-site differences in plasma concentrations, with the concentrations being the highest following application to the chest and lowest when applied to the upper outer thigh. (Hadgraft Decl., ¶ 15 (Exh. B))

The Hopkins et al. study is important for at least two reasons. First, if the chest, upper arm and outer thigh all have different permeabilities (with the permeability of the chest being significantly higher than that of the outer thigh), Catapres TTS, with its so-called rate-controlling membrane, should have delivered clonidine at the same rate at each site. The results suggest instead that the skin is more significant than the transdermal system in controlling input. (Hadgraft Decl., ¶ 15 (Exh. B)) Second, the study results evidence the difficulty of defining what exactly is "high permeability" skin. Based on the study results, the chest was significantly more permeable than the outer thigh. But how much higher than chest permeability is the permeability of the "person with highly permeable skin?"

iii. Additional clinical studies suggesting that the rate control membrane in Catapres TTS does not provide rate control are those that have shown the high degree of variability (25%-80%) in the amount of clonidine delivered from Catapres TTS.[11] (Hadgraft Decl., ¶ 16 (Exh. B))

3. A Comparison of the Contributions of Mylan CTS and Catapres TTS Versus the Skin to the Control of Drug Delivery Show That Mylan CTS Provides Equal or Better Rate Control Than Catapres TTS

Mathematical models are ideal for determining the relative control of drug delivery by a transdermal system as compared to the skin. Hadgraft and Guy[12] describe the relative resistances

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[11] Klein, MD, Am J. Emergency Medicine 17:2, 175-76 (1998) ("The pharmacokinetics of dermal absorption from a patch is variable and the amount of residual drug persisting after several days of use ranges from 20% to 75% . . .") (Exh. H); Caravati, EM, Annals of Emergency Medicine 17:2, 175-76 (1998) ("The amount of residual drug in the system after seven days of use may vary from 20% to 75% . . .") (Exh I); McGregor, TR et al., Clin Pharmacol Ther 38:278-84 (1985) (Exh. J).

[12] Guy, RH, and Hadgraft, J, Rate Control in Transdermal Drug Delivery? Int. J. Pharmaceut., 82, R1-R6, 1992 (Exh. K).

to drug diffusion contributed by a transdermal system and the skin. Their work compares nitroglycerin systems with and without rate-controlling membranes. Their work provides a model by which the relative portion of the control of drug delivery that is associated with the transdermal system and the skin can be estimated. Dr. Hadgraft describes in his Declaration various calculations performed using different data sets, to determine the relative control of drug delivery provided by Catapres TTS and Mylan CTS versus the skin. Dr. Hadgraft also calculates the "enhancement factor" for high permeability skin.

When applied to experimental data for Mylan CTS and Catapres TTS, the Hadgraft and Guy model demonstrates that Mylan CTS possesses better rate control than Catapres TTS, both for normal skin and compromised skin. (Hadgraft Decl., ¶¶ 18-20 (Exh. B))

Alza's own data also show that the so-called rate-controlling membrane in Catapres TTS does not control the rate of skin permeation. Using data from Enscore et al., "Structure and Function of Catapres-TTS" (1985) (Exhibit S to BI's February 20, 2002 Supplement)[13] in the Hadgraft and Guy model shows a 53% contribution of Catapres TTS (and 47% for skin) to control of drug delivery. The Hadgraft and Guy model also shows the enhancement factor in highly permeable skin to be about the same for Catapres TTS and Mylan CTS, thus indicating similar mechanisms of delivery for the two systems. (Hadgraft Decl., ¶ 21 (Exh. B))

Similarly, using the Hadgraft and Guy model with data obtained by Toon et al. shows only a 37% contribution to control of drug delivery from Catapres TTS (and 63% from skin). (Hadgraft Decl., ¶ 22 (Exh. B)) This figure is consistent with industry views of membrane-controlled systems generally. See Berner et al., "Pharmacokinetic Characterization of Transdermal Delivery Systems," Clin. Pharmacokinetics 26(2):121-34, 130 (1994) ("In practice, few membrane-controlled systems contribute even 30% of the total control of drug flux from the system over the lifetime of the system.") (Exh. L).

In addition, the Hadgraft and Guy model is validated by studies of Govil et al. (Pharmaceutical Research 4(2):S-71 (1987) (Exh. M)), comparing nitroglycerin (GTN) transdermal systems, with and without a rate control membrane. (Hadgraft Decl., ¶ 23-24 (Exh. B))

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[13] BI cites Enscore et al. (on page 3 of the February 20, 2002 Supplement) for the proposition that "[t]he rate-controlling membrane in the Catapres-TTS controls the rate of drug input to the blood stream, minimizing the intra- and inter- patient variability in the dose of drug received which could result if skin, with its inherent variability in permeability, were allowed to control the rate of drug input."

F. Adhesive Cold Flow Does Not Occur With Mylan CTS

Adhesive cold flow does not occur with Mylan CTS.

Mylan CTS includes zinc oxide (ZnO), which performs the same function as the silicon dioxide in Catapres TTS. In particular, both materials are physiologically inert and serve to stiffen the adhesive matrix, thereby providing resistance to cold flow.

Additionally, there was no evidence of adhesive cold flow in Mylan's extensive stability studies, as well as no evidence of adhesive transfer to the inside surface of the pouch surface.

G. A Drug Content Within 10% of the NDA-Approved Transdermal System is Not Required For Approval of a Generic Transdermal System

A drug content within 10% of the NDA-approved transdermal system is not required.

Transdermal systems are not intended for oral administration of drugs. With transdermal systems (whether or not they contain a rate control membrane), not all of the drug in the system is delivered to the patient. Therefore, the amount of drug contained in the system should not be relevant to approval.

Furthermore, drugs administered transdermally must be in solution to be absorbed by skin. Thus, the excess solid drug contained in Mylan CTS presents no greater safety hazard than Catapres TTS. Both Mylan CTS and Catapres TTS contain several fold more drug than the actual amount delivered to the patient over the 7-day use period.

Section 505(j)(2)(A)(iii) of FFDCA requires that the route of administration, the dosage form and the strength of the generic and reference drug be the same. In the case of oral dosage forms, strength and drug content are the same. However, for transdermal products, "strength" is the rate of administration. Examples include systems containing nitroglycerin and estradiol. TransdermNitro (0.2 mg/hr strength) contains 25 mg of nitroglycerin, while the approved generic equivalent contains 22.4 mg of drug for the same product strength. NitroDur (0.2 mg/hr strength) contains 40 mg of nitroglycerin, while the approved generic equivalent contains 21 mg of drug for the same product strength. Similarly, Climara, a reference listed patch, contains 7.6 mg of estradiol for the 0.1mg/day product strength, while the approved generic equivalent contains 3.88 mg for the same product strength. The "strengths" of Mylan CTS and Catapres TTS are the same.

In addition, all transdermal systems contain amounts of drug in excess of the dose delivered to the patient. Indeed, this is true for Catapres TTS. See BI Citizen Petition, at 3 ("To

ensure constant release of drug over seven days, the total drug content of the system is sufficiently greater than the total amount delivered that the concentration of drug in the reservoir and the skin-contact adhesive is above saturation during the seven-day application period.") In addition, any safety concerns regarding accidental ingestion of residual drug have been addressed in the product labeling instructions for disposal of used patches. Such labeling has been satisfactory for transdermal systems containing potent drugs, such as fentanyl in Duragesic transdermal systems.

H. A Difference in Mineral Oil/Polyisobutylene Ratio Does Not Increase the Sensitization Potential of Mylan CTS

BI argues that the burden is on Mylan to show that the change in the mineral oil/polyisobutylene ratio does not result in a less biocompatible adhesive that could lead to increased skin sensitization or other adverse effects. February 20, 2002 Supplement, at 10. However, Mylan CTS has been evaluated against Catapres TTS in the recommended FDA sensitization protocol, the results of which showed that Mylan CTS has no greater potential for sensitization than Catapres TTS.

CONCLUSION

For all of the foregoing additional reasons, the Citizen Petition should be denied.

Respectfully submitted,

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Enclosures

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