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VIA FEDERAL EXPRESS

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

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

Dear Sir or Madam:

We submit this supplement to the above-referenced citizen petition (the "Petition") on behalf of our client, Boehringer Ingelheim Pharmaceuticals, Inc. ("BI"). BI is the developer and marketer of Catapres-TTS® clonidine transdermal therapeutic systems (hereinafter, "the BI patch").

We are submitting this supplement for two purposes. First, we want to clarify, focus, and further support an important point made in the Petition – a clonidine transdermal patch that lacks a rate-limiting barrier is a radical departure from the BI patch and cannot be approved under an ANDA. Second, we want to address the issues raised by the filing of a new ANDA for a clonidine transdermal patch.

A. Monolith Patches Are Too Different from the BI Patch To Be Approved Under an ANDA.

In the Petition, BI addressed the implications of not having a rate-controlling membrane in a clonidine transdermal product. The Petition argued that 1) a patch without a rate-controlling membrane should not be approved under an ANDA based on bioequivalence testing comparing it to the BI patch and 2) no generic version should be approved without successful completion of the type of bioequivalence testing described in the Petition.

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This Supplement, prepared after consultation with top scientific experts in the relevant disciplines, is intended to support and expand on the first point. In particular, this supplement addresses why a monolith patch should not be approved under an ANDA, even if it is determined to be bioequivalent to the BI patch in the type of bioequivalence test described in the Petition.

The reason for this concern is explained below:

The ANDA Products Represent a Rejection of the Safeguards of TTS Technology

Because clonidine is so potent, and is recognized as a drug with a narrow therapeutic index, it is crucial that the rate and extent of absorption of clonidine from a transdermal patch be carefully controlled. The BI patch provides that careful control through the TTS (Transdermal Therapeutic Systems) technology developed by the Alza Corporation.

The TTS technology was developed because of the understanding that, while the stratum corneum of the skin itself provides some control over the absorption of drug through the skin, that control is too variable to be adequate for a potent drug. To quote an early review:

> [T]he inherent permeability of skin to a particular drug formulation varies at different sites of each individual (Feldmann and Maibach, 1967) and at the same site of different individuals. The permeability of normal skin also varies between sexes and among different age and ethnic groups (Montagna, et al., 1972; Zbinden, 1976). Moreover, changes in environmental conditions and physiological variations in skin blood flow and sweat gland function can change skin permeability.

Shaw, JE and Chandrasekaran, SK, Transdermal Therapeutic Systems. In Prescott et al. (eds.) Drug Absorption, pp. 186-193 at 186, ADIS Press: New York, 1981 (Exhibit R).

> To ensure that the system, and not the skin, controls the administration of drug to the systemic circulation, the system must deliver less drug per unit area than the skin is capable of absorbing . . . .

Id. at 187.

> If skin is the controlling factor, a combination of regional differences in skin temperature and inter- and intra-individual differences in skin permeability are responsible for the marked variations in systematic absorption of a drug following topical administration. For drugs with a narrow therapeutic index — for which there must only be a small variation in systemic absorption, not only within but also between individuals — control of drug input must not reside within the skin, but within the dosage form.

Id. at 192.

This theory is implemented in the BI patch. Thus,

> [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.

Enscore, DJ, Chu, LC and Shaw, JE, Structure and Function of Catapres-TTS. In Weber et al. (eds) Low Dose Oral and Transdermal Therapy of Hypertension at pp. 114-117, Steinkopff, Darmstadt, 1985 at 116-117, (Exhibit S).

The ANDAs from Elan Pharmaceutical Research Corp. ("Elan") and Mylan Technologies, Inc. ("Mylan") (which is discussed below) that seek approval based on the BI Catapres-TTS patch represent a rejection of the technology that went into the development of this product. It is not clear whether they in fact rely on the skin to control drug input. If they do rely, in whole or in part, on the skin and are nevertheless able to "pass" a bioequivalence test versus the BI patch, it is likely only because the controlled environment of the test,[1] which may not include individuals with high skin

[1] In this context, the fact that any "failed" bioequivalence tests for these products would not be submitted to FDA is particularly disturbing.

permeability, allowed a showing of equivalence that is highly unlikely to be duplicated in actual use.

Operation of the Patches

The BI patch is described in the Petition and in the declaration of Harold B. Hopfenberg, Ph.D., which is attached to this Supplement as Exhibit T. Essentially, the BI patch consists of four layers (plus a protective liner that is removed when the product is applied): a backing, a drug reservoir, a rate-controlling membrane, and an adhesive layer. Clonidine is contained in the drug reservoir and in the adhesive layer as a saturated solution, with the concentration of undissolved excess clonidine being much higher in the reservoir. See declaration of Dr. Hopfenberg, ¶ 6. When the liner is removed and the patch is applied to the skin, clonidine from the saturated solution in the adhesive layer diffuses into the stratum corneum layer of the skin as a loading dose. When that layer becomes filled, the clonidine diffuses into lower layers of the skin and into capillaries. When the concentration of clonidine in the adhesive layer falls below saturation levels, clonidine begins to flow from the reservoir to the adhesive layer through the rate-controlling membrane at a rate limited by that membrane. See declaration of Dr. Hopfenberg, ¶ 9. Thus, after the initial loading dose, the rate of diffusion from the adhesive layer to the skin cannot exceed the rate of diffusion from the reservoir to the adhesive layer. See Enscore, DJ, Osborne, JL and Shaw, JE, *In Vitro/In Vivo* Functionality of Catapres-TTS®. Meth and Find Exp Clin Pharmacol 1989, 11(3), 173-178, at 175 (Exhibit V).

This picture changes dramatically in the case of a monolith patch. With such a patch, there is no rate-controlling membrane. Accordingly, unless the ANDA applicant has developed its own, different technology that does not rely at all on the skin, the resistance limiting diffusion would be affected by the permeability of the skin itself. See declaration of Dr. Hopfenberg, ¶ 13. That would be expected to mean that, unless the skin itself provides an effective rate-limiting barrier, a monolith patch could deliver drug at a different rate than the Catapres-TTS patch, i.e., more drug would pass into the body soon after application and (if the drug in the patch is thus depleted) less would enter the body after a period of wear. This underscores the importance of the type of bioequivalence testing the Petition advocates — testing that would assure that the amount of drug administered at each relevant point during the use of the generic patch is the same as occurs with the BI patch.

For a drug as potent as clonidine, failure to require a showing that the generic product produces and maintains the same steady-state drug levels as the BI patch would be a dangerous mistake. We thus expect that FDA would in fact require such a showing in a bioequivalence test. There is a reason for concern, however, that even the type of test described in our Petition – which we believe is appropriate to compare two products that use the same rate-limiting barrier technology – would be inadequate to assure equivalency of a monolith patch to the BI patch.

If a monolith patch matches the BI patch in bioavailability, that may only be because, in the subjects included in the bioequivalence test, the skin of the subject provided the necessary resistance to permeation. See declaration of Dr. Hopfenberg, ¶ 13. If that occurred, however, there would be a significant risk that the generic patch without a rate-controlling barrier, though "bioequivalent" to the BI patch in the test subjects, could be dangerously bioinequivalent among patients with higher than average skin permeability. See declaration of Howard I. Maibach, M.D., ¶ 7 (Exhibit V to this Petition). See declaration of Dr. Hopfenberg, ¶ 15.

Role of the Skin and its Permeability

The characteristics of the skin are not uniform from individual to individual. As discussed in the declaration of Dr. Maibach, the permeability of people's skin varies. See also Shaw, JE, Cramer, MP and Gale, R, Rate-Controlled Transdermal Therapy Utilizing Polymeric Membranes. In Kydonieus AF and Berner B (eds), Transdermal Delivery of Drugs (Volume I), pp. 102-116 at 109, CRC Press, Inc. Boca Raton, Florida. 1987 (Exhibit W). There is a spectrum of permeability ranging from "normal" levels to high permeability. If an individual's skin permeability is high, that individual's skin would offer less resistance to diffusion of a drug delivered transdermally.

If there is significant variation in permeability among individuals, that variation may be reflected in differences in rates of absorption of drugs like clonidine. For patients with high skin permeability, the skin would offer less resistance. See declaration of Dr. Hopfenberg, ¶ 13. In such a situation, the rate of drug diffusion from the adhesive layer would increase. If such patients were to use the BI patch, however, one would not expect to see a significant increase in rate of delivery to the plasma because that rate would ultimately be controlled by the rate of diffusion from the reservoir to the adhesive layer (which is limited by the rate-controlling membrane). If the patient uses a patch that relies, in whole or in part, on the skin as its rate-controlling mechanism, on the other

hand, the higher permeability of the skin would be reflected in an increased rate of drug delivery.[2]

The net result of this situation is that the drug will be delivered from such a patch at a greater rate to individuals with higher skin permeability than to individuals with lower skin permeability. See Shaw, JE, Cramer, MP and Gale, R., Rate-Controlled Transdermal Therapy Utilizing Polymeric Membranes, at 105.[3] Drug delivery to patients

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[2] See declaration of Dr. Hopfenberg, ¶¶ 14-15:

> 14. Suppose, therefore, that one performed a bioequivalence study involving persons with normal skin permeability comparing the Catapres-TTS system to a monolith patch. One would anticipate, assuming the sizing, ingredients, etc., were adjusted appropriately, that a monolith patch could pass a standard bioequivalence test. This is because, for all of the test subjects with average skin permeability, the stratum corneum would contribute to the overall resistance limiting drug administration, thereby moderating the rate of net drug delivery from the monolith.
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> 15. If the same two patches were tested in persons with highly permeable skin, however, they might not be bioequivalent. This is because the maximum rate of delivery of the clonidine to the person with the highly permeable skin would be expected to be much higher from the monolith patch than the maximum rate from the Catapres-TTS system with a rate-controlling membrane. Because of the extraordinary potency of clonidine, the absence of a rate-controlling membrane could present a serious safety problem.

[3] See id at 105:

> In practice, this has been approached by delivery of the drug from the dosage form at a rate that is below the rate at which the drug can permeate even the most impermeable skin. The obverse situation, where the drug is released much faster than the skin can accept it, makes the variable barrier properties of skin the determinant of the systemic dosage. In such a situation patients with highly permeable skin will absorb much larger doses than

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using the BI patch, on the other hand, would be limited to the rate at which the drug would flow through the rate-controlling membrane. See generally Hopfenberg declaration.

The difference in performance of Catapres-TTS patches and patches dependent on the skin for rate control could be even greater with increased activity of the patient. Studies have shown that absorption from a transdermal product increases with exercise. See Klemsdal, TO, Gjesdal, K and Zahlsen, K, Physical exercise increases plasma concentrations of nicotine during treatment with a nicotine patch. Br J Clin Pharmac 1995, 39, 677-679; (Exhibit X). Sebel, PS, Barrett, CW, Kirk, CJC, and Heykants, J, Transdermal Absorption of Fentanyl and Sufentanil in Man. Eur J Clin Pharmacol 1987, 32, 529-531 (Exhibit Y). While the cause of this effect is not known for certain, experts such as Dr. Maibach believe that it is due to increased blood flow to the area under the patch. See declaration of Dr. Maibach, ¶ 8. Similarly, changes in temperature could also affect permeability. See Klemsdal, TO, Gjesdal, K, and Bredesen, JE, Heating and Cooling of the Nitroglycerin Patch Application Area Modify the Plasma Level of Nitroglycerin. Eur J Clin Pharmacol, 1992, 43, 625-628 (Exhibit Z). Any significant increase in plasma levels of clonidine may have clinical significance because of the potency of clonidine, a narrow therapeutic index drug.

Significance for Demonstrating Safety and Effectiveness

In the Petition, BI argued that generic transdermal clonidine products that are considered for approval under ANDAs should be subject to the same bioequivalence test as was performed by BI when it changed manufacturing sites for the Catapres-TTS product. That test is intended for patches of similar design to the BI Patch – i.e., products with a rate-controlling membrane. Because of the potential for greater variation in rate of drug delivery with a patch dependent on the skin due to differences in skin characteristics, as the Petition states, such a patch should not be considered for approval under an ANDA without proof of the safety of its inactive ingredients (including the way those inactive ingredients are assembled in the product). Certainly, it would be

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others. Thus, for drugs with a narrow therapeutic window, a high degree of control must be vested in the system.

inappropriate to approve such a patch solely on the basis of the proposed (or any other) bioequivalence test.[4]

B. Mylan Paragraph IV Notice Letter

The Petition noted that it was prompted in part by a "paragraph IV" notice letter received by BI from Elan. After submitting the Petition, BI received a paragraph IV notice letter from Mylan.

1. The Mylan Notice Letter

Mylan sent a paragraph IV notice letter to BI and patent owner Alza Corporation. See letter from Shelly Montelcone, Esq., to Office of the General Counsel, Boehringer Ingelheim Pharmaceuticals, Inc., and Office of the General Counsel, ALZA Corporation, dated October 4, 2001 (hereinafter "Mylan notice")(attached as Exhibit BB to this Petition). In that notice, Mylan states that its proposed product is a "monolithic patch," and provides no explanation of how, if at all, the rate of drug delivery from its patch may be limited. Mylan asserts that its product contains clonidine, mineral oil, zinc oxide, Vistanex L-100, and Vistanex LM-MS-LC. Mylan argues that its product does not infringe ALZA's patent because its product does not include silicon dioxide and has a Mineral Oil/Polyisobutylene ratio of less than 1.0.

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[4] If FDA nonetheless believes that it is possible to design an appropriate bioequivalence test, it would be important that such a test address the potential differences in performance of the two types of patches. One consideration would be assuring that the population for the test includes a sufficient number of people with high permeability skin. FDA should also apply tighter controls than would be necessary if the generic product contained a rate-controlling barrier, such as to apply the 90-110% criteria discussed in the context of certain other narrow therapeutic index drugs. (FDA has classified clonidine transdermal patches as drugs with a narrow therapeutic index. See Guidance for Industry: Scale-Up and PostApproval Changes, Appendix A (Exhibit AA to this petition)). FDA might also consider addressing the potential differences by using an individual bioequivalence approach, though that would only work if subjects with highly permeable skin happened to be among the subjects of the study. None of these solutions, however, ultimately protect the public or conform to the law.

2. FDA Should Not Approve the Mylan Product Under an ANDA

The information available to BI concerning the Mylan patch is limited to that set out in the Mylan notice. Nevertheless, it appears clear that the Mylan product includes different inactive ingredients from those found in the BI patch and that there is a risk, which FDA must evaluate, that those different inactive ingredients undermine the safety or effectiveness of the product.

Lack of Rate-Controlling Barrier.

First, and perhaps most important, Mylan states explicitly that its patch "is a monolithic patch" (Mylan notice at 3). Monolith patches do not have rate-controlling membranes, and the Mylan product is thus much different in its controlled-release mechanism from the BI patch. Its use of a new release mechanism makes approval of the Mylan product under an ANDA inappropriate (see Petition, pg. 6). The arguments made in the Petition, and further addressed above, concerning the importance of the BI patch's rate-controlling barrier must be considered in the evaluation of the Mylan patch.

Absence of Silicone Dioxide.

Mylan, in its notice, asserts that its product does not contain silicone dioxide. Silicone dioxide prevents "cold flow" of the clonidine-containing adhesive in the patch. This is a safety-related issue because cold flow of the drug substance could result in contamination of the patient's hands and, if the patient rubbed his or her eyes, that could result in potentially dangerous blurred vision. Thus, the burden is on Mylan to show that its combination of inactive ingredients would not be less safe than the combination of ingredients found in the BI patch.

Difference in Ratio of Mineral Oil to Polyisobutylene.

Mylan, in its notice, also makes a point of arguing that its product contains a ratio of polyisobutylene (an adhesive chosen for its biocompatability) to mineral oil that is lower than the ratio of those two ingredients found in the BI patch. Again, the burden is on Mylan to show that this change in the ratio of these important inactive ingredients does not result in a less biocompatible adhesive that could lead to increased skin sensitization or other adverse effects.

Ultimately, the Mylan product is a new combination of inactive ingredients with the active ingredient found in the BI patch. As such, unless Mylan shows that its combination of inactive components do not raise issues of safety and effectiveness, this much different drug cannot be approved under an ANDA referencing the BI patch.

3. FDA Should Apply to the Mylan Product the Standards Set Forth in the Petition

In the Petition, BI explained its concerns regarding patch products referencing the BI patch that may differ in composition or may not be subject to the same bioequivalence requirements. Those concerns all apply to the Mylan product.

CONCLUSION

For the reasons discussed in the Petition and in this Supplement to the Petition, BI submits that FDA should grant the Petition in all aspects.

Sincerely,

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EXHIBITS TO FEBRUARY 20, 2002 SUPPLEMENT TO CITIZEN PETITION OF BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. DOCKET NO. 01P-0470

INDEX OF EXHIBITS

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R.	Shaw, JE and Chandrasekaran, SK, Transdermal Therapeutic Systems. In Prescott et al. (eds.) Drug Absorption, pp. 186-193, ADIS Press: New York, 1981.
S.	Enscore, DJ, Chu, LC and Shaw, JE, Structure and Function of Catapres-TTS. In Weber et al. (eds.) Low Dose Oral and Transdermal Therapy of Hypertension at pp. 114-117, Steinkopff, Darmstadt, 1985.
T.	Declaration of Harold B. Hopfenberg, Ph.D.
U.	Enscore, DJ, Osborne, JL and Shaw, JE, *In Vitro/In Vivo* Functionality of Catapres-TTS®. Meth and Find Exp Clin Pharmacol 1989, 11(3), 173-178.
V.	Declaration of Howard U. Maibach, M.D.
W.	Shaw, JE, Cramer, MP and Gale, R, Rate-Controlled Transdermal Therapy Utilizing Polymeric Membranes. In Kydonieus AF and Berner B (eds), Transdermal Delivery of Drugs (Volume I), pp. 102-116, CRC Press, Inc. Boca Raton, Florida, 1987.
X.	Klemsdal, TO, Gjesdal, K and Zahlsen, K, Physical exercise increases plasma concentrations of nicotine during treatment with a nicotine patch. Br J Clin Pharmac 1995, 39, 677-679.
Y.	Sebel, PS, Barrett, CW, Kirk, CJC, and Heykants, J, Transdermal Absorption of Fentanyl and Sufentanil in Man. Eur J Clin Pharmacol 1987, 32, 529-531.
Z.	Klemsdal, TO, Gjesdal, K, and Bredesen, JE, Heating and Cooling of the Nitroglycerin Patch Application Area Modify the Plasma Level of Nitroglycerin. Eur J Clin Pharmacol, 1992, 43, 625-628.
AA.	Guidance for Industry, "Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation."
BB.	Notice of Paragraph IV Certification: Letter Dated October 4, 2001 to Office of the General Counsel, Boehringer Ingelheim Pharmaceuticals, Inc., and Office of the General Counsel, Alza Corporation, from Shelly Monteleone, Esq., Mylan Technologies, Inc.