M E M O R A N D U M
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: **October 28, 2005**

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Subject: **CSS Consultation regarding sponsor resubmission for NDA 21-514 (methylphenidate transdermal system)**
Indication: treatment of attention deficit hyperactivity disorder
Application Due Date: December 28, 2005
Sponsor: Noven Pharmaceuticals

Background

New Drug Application (NDA) 21-514 was submitted by Noven Pharmaceuticals, Inc. (Noven) on 27 June 2002 for the Methylphenidate Transdermal System (MTS) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients. MTS contains a mixture of *d*- and *l*-methylphenidate, an approved agent for the treatment of ADHD, in a multi-polymeric adhesive platform, as a means of delivering methylphenidate transdermally during the period of patch wear.

Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine monoamines into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d*- and *l*-enantiomers. The *d*-enantiomer is more pharmacologically active than the *l*-enantiomer.

The methylphenidate transdermal system, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

On 10 October 2003, the Agency issued an approvable letter detailing the deficiencies of NDA 21-514. The Agency requested the Sponsor to address the high incidences of insomnia, anorexia, and significant weight loss noted in the short term studies. The FDA expressed concern that these adverse events could result in growth retardation or other serious adverse consequences with

chronic long term treatment with MTS. The Agency suggested that decreasing the wear time of the MTS patch might decrease insomnia, anorexia, and significant weight loss to acceptable levels. The Agency also requested a Risk Management Program be developed for the product.

CSS has been asked to review and comment on the resubmission.

Submission Review

The NDA can be found in the electronic document room (EDR). Data on the product submission was obtained utilizing the EDR and DFS. Sections on chemistry, pharmacokinetics, labeling (including abuse / dependence) and risk management were reviewed.

Product Description

The sponsor proposes 4 patch dosage sizes including 12.5 cm^2 (27.5 mg), 18.75 cm^2 (41.3 mg), 25 cm^2 (55 mg), and 37.5 cm^2 (82.5 mg). The actual amount of MPH delivered by the different patch strengths over 9 hours ranges from 10 mg for the smallest patch to 27 mg for the largest. MPH is contained in the adhesive formulation utilizing DOT Matrix® transdermal technology, consisting of an acrylic adhesive, a silicone adhesive and methylphenidate. Release of active drug from the adhesive matrix is constant over time, with no rapid release component when the patch is initially applied. The total amount of drug absorbed transdermally is determined by the surface area (size) of the patch (ie. amount of adhesive/methylphenidate exposed to the skin).

All 4 patch sizes of this product contain 1 ½ times more methylphenidate then Concerta®, the controlled release oral formulation utilized by the sponsor to compare safety and efficacy. Comparable Concerta® dosages include 18 mg, 27 mg, 36 mg, & 54 mg. (See Synopsis Table VII on next page)

Table 1 and Table VII are taken from the Sponsor submission. The data indicates that for "comparable" dosing, the patch results in doubling of the mean 9 hour plasma concentration of *d*-MPH when compared to Concerta®. This level is sustained at a steady state until the patch is removed and then decreases over a 2-3 hour period.

TABLE 1

Mean ± SD Plasma *d*-Methylphenidate (Sample taken at 9 hrs after application)

Pharmacokinetic Parameters After Repeated 9-Hour Applications of [TRADEMARK] for 7 Days

Parameters	12.5 cm^2 (N = 7)	18.75 cm^2 (N = 32)	25 cm^2 (N = 27)	37.5 cm^2 (N = 8)
C_{max} (ng/mL)	20.0 ±11.1	23.9 ±8.9	30.5±16.0	46.5 ±27.3
T_{max} (hrs)*	7.1 (4.3 – 8.8)	8.0 (5.7-11.8)	8.8 (5.8 –11.7)	8.8 (7.3 – 10.3)
AUC_{0-t} (ng·hr/mL)	139±95.2	171 ±78.1	225 ±139.0	332 ±254.0

* Median (range)

The patch contains a racemic mixture of *d*-MPH and *l*-MPH. Concerta® contains only *d*-MPH. In addition to the already mentioned doubling of *d*-MPH levels, there is also a significant plasma concentration of *l*-MPH which results from application of the patch. The following table taken from the submission illustrates this:

Synopsis Table VII: Mean (SD) 9 hour plasma *d*- and *l*-MPH concentrations (ng/mL) for MTS and CONCERTA

Patch Size	*d*-MPH	*l*-MPH	Capsule Strength	*d*-MPH	*l*-MPH
12.5cm2	12.7	6.87	18mg	8.65	0.00
(N=5)	(7.42)	(4.09)	(N=3)	(1.75)	(0.00)
18.75cm2	20.1	10.0	27mg	11.0	0.852
(N=14)	(15.3)	(7.08)	(N=13)	(9.48)	(2.31)
25cm2	38.6	20.2	36mg	20.1	0.178
(N=20)	(17.0)	(8.64)	(N=23)	(9.77)	(0.322)
37.5cm2	47.0	28.6	54mg	23.2	0.337
(N=33)	(27.1)	(20.6)	(N=41)	(13.2)	(0.618)

Abuse Potential

There is no initial rapid release component of the patch. Onset of action is 2-3 hours after transdermal application of the patch as prescribed. Theoretically, this may make this product less of an attraction to an abuser because there would be no "rush" from applying the patch. Similarly, "sharing" a patch would entail a 2-3 hour delay before the 2nd user would perceive any drug effect, while the initial user would not have the patch available to maintain a drug effect.

The total amount of methylphenidate in each patch appears large when compared to oral dosing forms of MPH (IR forms contain up to 20 mg and ER forms up to 54 mg). However, the matrix formulation of the patch prevents easy access to this total drug content and lessens the risk of the drug being accessible for dissolution and injection or for rapid release. This decreases the safety concerns associated with misuse and abuse of the intact product. The method in which the methylphenidate is contained in the adhesive portion of the patch requires complex chemical extractions to obtain an abusable form of the drug. This procedure would be lengthy and expensive and most likely not worth the time or trouble by an abuser, due to the small yield of drug from a patch. The sponsor indicates that exposing the patch to alcohol does release from the product but not at levels which would be abusable or raise safety issues. Similarly, it would be unlikely that an abuser would want to cut and chew the patch due to the relatively small total amount of drug contained in the patch. The greater abuse concern would be diversion of this product. For example, a patient might share a single patch with someone else, unlike an oral dosage form, which can only be ingested by one person.

Drug Dependence

The risk associated with abuse, misuse, or addiction (substance or drug dependence) from the methylphenidate transdermal patch will likely be similar to other formulations of methylphenidate.

The following is the black box warning statement contained in the proposed drug labeling:

Drug Dependence
[TRADEMARK] should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abuse can lead to marked tolerance and physiological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

A similar black box warning appears in the Ritalin label:

Drug Dependence

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

Because the proposed warning is based on information obtained from an older drug product, it includes out-of-date terminology and concepts, and fails to address current issues regarding the safety of this drug.

If the sponsor includes information in the black box warning specifically mentioning the possibility of severe depression if the drug is withdrawn, then this issue needs to be addressed specifically in both the Risk Management Program and the labeling / patient information. In view of the recent FDA warning regarding Strattera® and suicide, the black box warning for this product should be updated, with this issue addressed.

Risk Management Program

The Risk Management Program was also reviewed. The goal of the Program as stated on the first page of the document is to provide a comprehensive approach towards reducing and detecting abuse and diversion of the product. No mention is made of risks regarding the safety of the product, such as overdose or misuse.

The Risk Management Program contains sections on packaging and the charting system printed on the package, disposal methods, school/community monitoring, internet monitoring program, news/media monitoring, federal surveys monitoring, supply chain monitoring, supplementary educational materials, sales representative training, risk management coordinator, and providing a toll free number. These sections are described generically, and have varying degrees of importance for risks associated with a stimulant type drug. Most of the sections describe a method to collect data, but do not indicate how this data will be used to promote the safe use of the product.

This Program was compared to the actual labeling section containing "Information for Parents or Caregivers". Although a section of the Risk Management Program defines a Charting System to be printed on the packaging as a method of tracking individual patch use, no instructions are provided in the labeling explaining how a parent is to utilize the chart.

The Risk Management Program describes the creation of a Risk Management Coordinator position, but does not clearly define the role of this person in relationship to reporting data between the sponsor and the FDA.

Conclusions

The abuse potential of the methylphenidate patch should be similar to other MPH formulations. The abuse potential of an individual patch, due to the relatively small of amount of drug in each patch, compared to reported amounts utilized by abusers, and the difficulty of extracting that drug into an abusable form, is not a large cause for concern. Diversion of the intact product would have a higher risk of abuse potential. While easy to share a patch, the long delay in reaching peak drug effect, would make this type of abuse less likely.

Recommendations

Label

The black box warning concerning Drug Dependence needs updating. It is copied from the Ritalin package insert, which is out of date, and does not address specific product properties. For example, "Frank psychotic episodes can occur, especially with parenteral abuse," is not relevant as this product can not be administered parenterally.

Sponsor should specify or study how drug release and absorption is affected by heat (internal or external), exercise and activity level and adhesion problems. Several safety issues were raised in a previous CSS consult (4/3/03), which have yet to be addressed by the current labeling. These involve varying patch properties while being worn by the patient. For example, will a patch applied to a child with a fever release a higher amount of drug? Similarly, how does physical activity, such as after school sports or physical education during school affect the amount of drug which is released? If a patch seems to be loose, what action does the sponsor recommend? If an occlusive dressing is recommended, how will this effect the drug release properties of the patch?

Labeling for the Patient

A section must be added to the labeling for the patient, where instructions are given on how to utilize the tracking chart provided on the side of the box in which the product will be dispensed. It would also be helpful to track the use of the product by having the sponsor collect the completed box charts from the parent, when the box is empty, perhaps as a requirement to obtain another box.

The labeling for the patient should also include clear instructions on the 9 hour recommended wear time for the product. This could be accomplished by providing instructions to write down time of application and at the same time "calculate" and write down the removal time.

Risk Management Program

The proposed risk management program is broad and general in scope, designed to address issues of abuse and diversion, but not of drug safety, specifically the risks of misuse and potential overdose. Further clarification is needed regarding how the various components of the program will actually impact the risk of this product. For example, the role of the risk management coordinator, a liaison position to interface with the various stakeholders, must be clearly defined,

including method and frequency of reporting data to the FDA. Specific educational programs must be developed for both the physician and the patient (and families) to address the safety concerns of using a stimulant chronically.