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APPLICATION NUMBER:
202100Orig1s000

PHARMACOLOGY REVIEW(S)

Pharmacology Toxicology Memo

NDA 202100

Sponsor: NextWave Pharmaceuticals

Supporting Document #: 19 (Response to FDA Complete Response Letter, Class 2 Resubmission)

Submission Date: 3/30/2012

Drug: Quillivant (methylphenidate hydrochloride) extended-release oral suspension

Indication: Attention deficit disorder (ADHD)

Reviewer: Ikram Elayan, Ph.D.

Supervisor: Linda Fossom, Ph.D.

Background:

This NDA is a 505 (b)(2) application that was reviewed from a preclinical perspective during the first cycle (review finalized on 5/09/2011) and was considered to be approvable. The NDA was not approved based on deficiencies identified during inspection of the manufacturing facility by the Office of Compliance (OC). A Complete Response (CR) letter was issued (8/30/2011).

The current submission contains a response to the CR letter and no new preclinical data were submitted. The Chemistry/OC deficiencies have been adequately addressed and there are no chemistry issues that would require additional non-clinical studies.

Recommendations:

From a preclinical point of view there are no issues to be addressed for this submission and the NDA may be approved.

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/s/

IKRAM M ELAYAN
08/15/2012

LINDA H FOSSOM
08/15/2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 202100
Supporting document/s: N-000
Applicant's letter date: 7/29/2010
CDER stamp date: 7/29/2010
Product: Methylphenidate HCl extended release powder
for oral suspension
Indication: Attention Deficit Hyper Activity Disorder (ADHD)
Applicant: NextWave Pharmaceuticals, Inc.
Review Division: Division of Psychiatry Drug Products
Reviewer: Ikram Elayan, Ph.D.
Supervisor/Team Leader: Linda Fossom, Ph.D.
Division Director: Thomas Laughren, M.D.
Project Manager: Shin-Ye, Chang, Pharm.D.

Disclaimer

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1 Executive Summary:

1.1 Introduction

This submission is a 505 (b)(2) application for the marketing of methylphenidate HCl Extended Release Powder for oral suspension. The Reference Listed Drug for this application is Methylin (methylphenidate HCl) Oral Solution (NDA 21-419). The Sponsor is proposing to use this product as a “pediatric-friendly” formulation for the treatment of attention deficit hyperactivity disorder (ADHD).

1.2 Brief Discussion of Nonclinical Findings

The current submission did not contain any new preclinical data for review; however, some chemistry related issues regarding impurities and excipients are discussed here from a pharmacology/toxicology perspective related to qualification and/or acceptance of their levels in the drug product or drug substance.

There were no safety concerns regarding any impurities or solvents. The levels of one excipient ((b) (4)) were slightly higher in this product than other previously approved products ((b) (4) in this product vs. up to (b) (4) , a previously approved product). In addition, this compound is used as an active ingredient at doses up to 60 g daily for the treatment of hyperkalemia (in Kionex®, Kayexalate®). This compound is not expected to be absorbed systemically, and therefore its toxicity would be considered minimal especially taking into consideration its low levels as an inactive ingredient in this drug product. For more details regarding this compound see the Integrated Summary at the end of this review.

1.3 Recommendations

1.3.1 Approvability

May be approved, from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

Nothing further.

1.3.3 Labeling

The results of a juvenile animal study for methylphenidate should be included in the labeling of this product.

The following is proposed labeling by the sponsor and the reviewer's comments are in italics:

Pediatric Use

[REDACTED] (b) (4)

The following is a description of the juvenile animal study that was described in the labeling of Ritalin (and Focalin), but not found in Methylin labeling. However, the results of the juvenile study conducted by Novartis have been published (Beckman et. al, Birth Defects Research (Part B), 83: 48-67, 2008)). The description of this study is to be added to the labeling for this product:

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of methylphenidate on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

Note: *The safety factors included above were based on a maximum dose of 2 mg/kg for children, which apparently was the "accepted" dosing paradigm for children in the earlier products of methylphenidate. Since the maximum recommend human dose (MRHD) for the product of this NDA is noted in labeling as 60 mg (for adults, adolescents, and children), the calculated safety factors based on this MRHD of 60 mg calculated on a mg/m² basis would be slightly lower (the safety factor for a dose of 50 mg/kg/day in animals would be ~4 instead of 6 and the safety factor for a dose of 100 mg/kg/day in animals would be ~8 instead of 12 when calculated on MRHD of 60 mg vs. 2 mg/kg in children). The reviewer believes that the difference is not drastically different and the same safety factors used in the old products can still be used for this product to*

maintain consistency between the different labeling of methylphenidate products. In addition, it seems likely that children are not often dosed up to 60 mg regardless of their body weight and the 2 mg/kg might still be of the practice in the clinics (the medical officer, Dr. Mark Ritter, was consulted in this regards and confirmed that the 2 mg/kg is still the dosing regimen used in children by clinicians).

Similar changes were also implemented in the labeling for the pregnancy and the carcinogenicity sections. The safety margins were calculated based on an MRHD of 2 mg/kg for adolescents (pregnancy section) or children (carcinogenicity section). The safety factors were based on a mg/m² basis.

Pregnancy

Pregnancy Category C

(b) (4)

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose on a mg/m² basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 5 times the maximum recommended human dose on a mg/m² basis.

The following is the description of the mechanism of action proposed for the product in this NDA (b) (4) :

Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant.

(b) (4)

The reviewer suggests the removal of the last paragraph, even though it might be acceptable for these products, it does not add any benefit to the interpretation of the mechanism of action for this product for this condition.

2 Drug Information

2.1 Drug

CAS Registry Number: 298-59-9

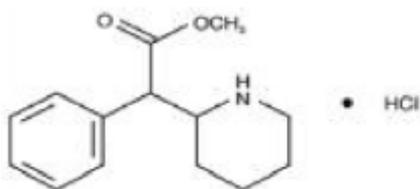
Generic Name: methylphenidate hydrochloride

Code Name: N/A

Chemical Name: methyl α -phenyl-2-piperidineacetate hydrochloride

Molecular Formula/Molecular Weight: C₁₄H₁₉NO₂.HCl/MW 269.77

Structure or Biochemical Description:



Pharmacologic Class: central nervous system stimulant

2.2 Relevant INDs and DMFs:

IND 73856 (IND for this NDA), NDA 21-419 (NDA of RLD Methylin), DMF (b) (4) for information on methylphenidate HCL USP, and DMF 23870 for information on drug product

2.3 Drug Formulation

Extended release powder for oral suspension (25 mg/5 ml in final dosing solution)

2.4 Comments on Novel Excipients

See Integrated Summary and Safety Evaluation below

2.5 Comments on Impurities/Degradants of Concern

See Integrated Summary and Safety Evaluation below

2.6 Proposed Clinical Population and Dosing Regimen

The drug will be indicated for the treatment of ADHD in patients aged 6 years and older.

2.7 Regulatory Background

The formulation for this NDA (extended release powder for oral suspension) was developed under IND 73856. The NDA for this formulation is a 505 (b)(2) with the Reference Listed Drug (RLD) being Methylin oral solution (NDA 21419). The Sponsor had two pre-IND meetings with the Division (May 8, 2006 and October 1, 2007) and an EOP-3 meeting (March 22, 2010). There were no preclinical issues discussed during these meetings, but some chemistry issues with excipients and impurities were discussed which might have indicated a need for pre-clinical evaluation for the qualification of these substances. This review is based on the CMC review for the evaluation of the levels of these substances and a preclinical evaluation is provided here as needed for their qualification.

3 Studies Submitted

No preclinical studies were submitted.

3.1 Studies Reviewed

No preclinical studies were submitted for review. However, based on the CMC evaluation for new excipients or impurities that might need to be qualified, this review was prepared.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

N/A

11 Integrated Summary and Safety Evaluation

Based on discussions with the Chemistry Review Team for this NDA and an evaluation of the chemistry review, it was clear that there were no concerns regarding the (b) (4) used in the manufacturing process. In addition there were no impurities at a level that requires qualification. However, (b) (4) which is present as an impurity in one of the excipients used (b) (4) (Poloxamer 188 NF), (b) (4); and has been demonstrated to be genotoxic and is considered to be a human carcinogen by the International Agency for Research of Cancer. According to the Chemistry Team, in the 60-mg drug dose (12 mL), the (b) (4) of excipient will contain no more than (b) (4) of (b) (4) per day which translates to no more than (b) (4). This level of (b) (4) is well below the allowable levels of a genotoxic impurity (1.5 mcg/day). Therefore, from a pharmacology/toxicology point of view there is no concern for the level of this genotoxic/carcinogenic substance present in the drug product.

Another excipient used in the drug product, polystyrene sulfonate sodium (b) (4), was present in previously approved products, (b) (4)

The Chemistry Reviewer for that NDA did not specify that excipient as a new excipient and stated that “the inactive ingredients used are commonly used”, and that “all inactive ingredients in the formulations except for dyes are listed in NF/USP”. There was no pharmacology/toxicology evaluation for that excipient under that NDA, possibly based on the chemistry conclusion of no new inactive ingredients. It should be mentioned that this compound is used as an active ingredient in Kionex®, Kayexalate® for the treatment of hyperkalemia at a dose ranging from 15 (b) (4) g/day. Additionally, this excipient was discussed under NDA 22500 (Clonidine HCl ER Tablets) and the Chemist reviewing that NDA stated that “The amount of sodium polystyrene sulfonate exceeds the inactive ingredient data base.” A pharmacology/toxicology evaluation for this excipient was done by Nick Jensen, Ph.D., as found in DARRTS. Dr. Jensen concluded that based on the summary data provided by the sponsor of NDA 22500 (summary data and unpublished data, no full study reports submitted for review), based on the fact that the ingredient was used in (b) (4) up to (b) (4) daily levels, and based on the human exposure to this compound as an active ingredient for the treatment of hyperkalemia with no indication of toxicity from available human data, the levels predicted from treatment with

the clonidine ER tablets which he calculated to be up to (b) (4) based on a total dose of 0.6 mg/day of clonidine, would be acceptable.

The reviewer of the current NDA agrees with the conclusions of Dr. Jensen. In addition, based on data submitted with the DMF accompanying this NDA (DMF 23870), the systemic absorption of a (b) (4) which is similar to the (b) (4) used in the drug product of the NDA of this submission, was (b) (4). Therefore, even though the data provided to qualify this inactive ingredient (provided as summaries in DMF 23870) were not optimal (only Ames test that used only four strains of bacteria, Segment II studies conducted in mice and rats but not rabbits, and no carcinogenicity testing), the fact that this compound is minimally absorbed might not require the usual evaluation of a novel excipient or any previously unqualified excipient with a predicted significant systemic exposure. The levels of this excipient in the product of this NDA (202100) are not largely different from those used in previous products (b) (4).

Even though the levels of this excipient in this product are (b) (4) than the previously approved products, this difference is not expected to result in different safety profile as discussed above.

(b) (4)

There are no pharmacology/toxicology issues that would prevent the approval of this NDA, assuming acceptable negotiation of labeling.

Ikram Elayan, Pharmacologist {see appended electronic signature page}

Linda Fossom, Pharmacologist/Team Leader {see appended electronic signature page}

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/s/

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05/09/2011

LINDA H FOSSOM
05/09/2011