CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207960Orig1s000

SUMMARY REVIEW

M E M O R A N D U M

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

Date	(electronic stamp)
From	Mitchell V. Mathis, MD
Subject	Division Director Summary Review
NDA/BLA #	207960
Applicant Name	Pfizer
Date of Submission	02/04/2015
PDUFA Goal Date	12/04/2015
Proprietary Name / Established (USAN) Name	QuilliChew ER/Methylphenidate HCl
Dosage Forms / Strength	Extended-release chewable tablet 20 mg, 30 mg, and 40 mg
Proposed Indication(s)	Attention Deficit Hyperactivity Disorder (ADHD)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Christina Burkhart, M.D.
Statistical Review	George Kordzakhia, Ph.D. Peiling Yang, Ph.D. H.M. James Hung, Ph.D.
Pharmacology Toxicology Review	Ikram Elayan, Ph.D. Linda Fossom, Ph.D.
CMC Review/OPQ Review	Gaetan Ladouceur, Ph.D Thomas Wong, Ph.D. Bogdan Kurtyka, Ph.D. Steven Fong, Ph.D. Salaheldin Hamed, Ph.D. Dahlia Woody, Ph.D. David Claffey, Ph.D.
Clinical Pharmacology Review	Huixia Zhang, Ph.D. Hao Zhu, Ph.D.
OPDP	Susannah O'Donnell, MPH, RAC
OSI	Jenn Sellers, M.D. Susan Thompson, M.D. Kassa Ayalew, M.D., MPH

OND=Office of New Drugs
OSI=Office of Scientific Investigation
OPQ=Office of Product Quality
OPDP=Office of Prescription Drug Promotion
CMC=Chemistry, Manufacturing, and Controls

Background and Summary

With this 505(b)(2) application, the applicant is seeking approval to market methylphenidate hydrochloride extended-release (ER) chewable tablet [MPH ERCT] for the treatment of attention deficit hyperactivity disorder (ADHD) in patients six to twelve years old. This formulation provides a once-daily treatment in a formulation that may be chewed; it is comprised of (b) (4)

The applicant submitted two studies to support their application:

- Study B7491004: Phase 1 relative bioavailability (BA) and effect of food study in healthy adults demonstrating bioequivalence (BE) between MPH ERCT and the listed drug Methylin IR chewable tablet (MPH IRCT).

- Study B7491005: Phase 3 laboratory classroom study of the safety and efficacy of MPH ERCT in pediatric patients (6-12 years old) with ADHD.

This sponsor failed to demonstrate BE to their suspension (methylphenidate ER suspension), and so the Division required an efficacy study to define the pharmacokinetic parameters of interest for a stimulant medication (e.g., Time to Onset of Effect, and Duration of Effect).

There was some disagreement with the applicant about an acceptable proprietary name for this product. A similar extended-release product available in a suspension (also owned by this applicant), Quillivant XR, was not BE to this formulation and so the Division objected to naming this product Quillivant Chewable for that reason. In addition, the USP definition of Chewable Tablet states that the product must be chewed, and this sponsor has some data that the PK profile is similar if the tablet is chewed or swallowed whole. In the end, it was decided that the proprietary name QuilliChew ER was acceptable.

Clinical Summary and Statistics

Efficacy

Drs. Christina Burkhart and George Kordzakhia conducted the clinical and statistical reviews, respectively. Dr. Kordzakhia concluded that efficacy of MPH ERCT was demonstrated in the Phase 3 trial which was a dose-optimized, randomized, double-blind, placebo-controlled laboratory classroom study (Study B7491005) conducted in the United States.

The pre-specified primary statistical analysis plan examined 20 mg – 60 mg (salt weight) by the model adjusted average of all post dose SKAMP Combined scores measured on the classroom Visit Day 9. Onset of efficacy was obvious statistically by 2 hours (the result at 0.75 hours was nominally statistically significant, but not after multiplicity adjustment) and efficacy was maintained through 8 hours.

Drs. Burkhart and Kordzakhia agree that efficacy was demonstrated and important pharmacodynamic parameters of interest identified, and I agree with them.

Safety
Methylphenidate has been a mainstay of ADHD treatment for many years and has a well-known safety profile. The findings from the Phase 3 study for this product were consistent with the known safety profile of methylphenidate. She recommended routine post-marketing surveillance and found no safety signals to preclude approval, and I agree with her.

Office of Clinical Pharmacology (OCP)
Dr. Huixia Zhang was the primary reviewer for this application. Her findings are summarized below.

- An adequate link has been established between the MPH ERCT and Methylin IRCT, the reference listed product.
- There would be different onsets and durations of clinical response expected upon product switching from Methylin IRCT to MPH ERCT or from MPH ER powder for oral suspension (Quillivant XR) to MPH ERCT.
- The indication of ADHD in adolescents and adults can be extrapolated from efficacy findings in children 6-12 years old without additional trials.
- The pharmacokinetic profile of MPH ERCT is consistent with ER formulations and is sufficient to support once-daily dosing.
- No significant accumulation is expected with multiple days of dosing.
- MPH ERCT can be (b) (4) chewed (b) (4).
- Food does not affect exposure.

OCP has recommended approval, and I agree with them.

Chemistry Manufacturing and Controls (CMC)
The CMC team recommended approval from a product quality perspective.

Office of Scientific Investigation—Facilities Inspections
OSI inspected two clinical sites and no significant regulatory violations were noted and the data were judged to be acceptable.

Office of Prescription Drug Promotion (OPDP)
OPDP reviewed the medication guide, the prescribing information, and the carton/container labeling and had several recommendations which were included in the final negotiated labels/container labeling.

Nonclinical Pharmacology/Toxicology
Drs. Elayan and Fossom conducted the nonclinical review. No new non-clinical data submitted with the application and no outstanding chemistry issues regarding impurities or new excipients were identified. They concluded that the application was approvable.

Labeling
The team constructed labeling based upon the data from this application. Comments/suggestions/edits from the team were considered and sent to the applicant multiple times for concurrence. The Office of Prescription Drug Promotion also reviewed the label and the

changes that they suggested were incorporated. The applicant has accepted the labeling changes and a final version will be attached to the letter.

Advisory Committee
Not applicable.

Postmarketing Requirements/Commitments
We have negotiated post-marketing requirements to conduct PK, efficacy and safety, and long-term safety studies in 4 to 5 years old patients with ADHD.

Conclusions
Sufficient information has been submitted to conclude that MPH ERCT is safe and effective for the treatment of pediatric patients with ADHD. I recommend that this application be approved.

The labeling has been negotiated to current Division standards.

Post-marketing requirements and commitments have been identified and agreed upon.

The applicant has agreed to the negotiated label.

This application will be approved by the PDUFA date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
12/04/2015