CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208277Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
1. Introduction/Regulatory Background

FYCOMPA® was approved as adjunctive therapy for treatment of partial-onset seizures (POS) with or without secondarily generalized seizures in patients aged 12 year and older under the original submission for NDA 202-834, and was later approved as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older under an efficacy supplement submission (NDA 202-834/s005).

Currently, the approved formulation is film-coated tablet with multiple strengths - 2, 4, 6, 8, 10 and 12 mg. The developed oral suspension (OS), 0.5mg/ml, is a follow-on product to the approved Fycompa tablets. It offers advantages for patients who are unable to swallow tablets. Additionally, although Fycompa is not currently approved for patients under 12 years old; the oral suspension is a potential dosage form for younger patients.

This submission does not contain a new efficacy or safety trial and the sponsor seeks OS approval solely relying on a pivotal bioequivalence (BE) study (Study E2007-A001-048) with supportive evidence from a population Pharmacokinetics (PK) analysis. The sponsor pursues the same indications for OS formulation as those approved for tablet.

The followings are the key primary reviewers for this NDA 208277:
- Clinical: Natalie Getzoff, M.D., Norman Hershkowitz, M.D., Ph.D.
- Clinical Pharmacology: Xinning Yang, Ph.D, Kevin Krudys, Ph.D., (Team Leader: Angela Yuxin Men, M.D., Ph.D.)
- Quality Review Team:
2. CMC/ Biopharmaceutics

From a CMC quality perspective, NDA 208277 for Fycompa® (perampanel) oral suspension is recommended for approval.

From a biopharmaceutics perspective, the following proposed dissolution method is acceptable:

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<tr>
<th>Apparatus</th>
<th>Speed</th>
<th>Volume and Medium</th>
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<tbody>
<tr>
<td>USP 2 (paddle)</td>
<td>50 rpm</td>
<td>900 mL [890 mL 0.1 M HCl + 10 mL perampanel oral suspension]</td>
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The dissolution acceptance criterion of $Q$ at 15 minutes for perampanel is acceptable. The Division of Biopharmaceutics recommends APPROVAL of NDA 208277 for Perampanel Oral Suspension, 0.5 mg/mL.

There are no Phase 4 commitments or agreements. The OPQ review team did not identify any issues that would require risk management steps.

3. Nonclinical Pharmacology/Toxicology
There is no updated information as the information in these fields remaining unchanged from those in the approved NDA.

4. Clinical Pharmacology

The clinical pharmacology review team evaluated the Pivotal PK study E2007-A001-048: “A Randomized, Open-Label, Crossover Study to Demonstrate Bioequivalence Between a 12 mg Dose of an Oral Suspension Formulation of Perampanel and a 12-mg Tablet Formulation of Perampanel Under Fasted and Fed Conditions in Healthy Subjects”. The results from Study 048 demonstrated that both rate and extent of absorption (Cmax and AUC) are BE between the OS and tablet formulations under fasted state. Under fed conditions, the extent of absorption (AUC) of the OS formulation was equivalent to the tablet formulation, whereas the rate of absorption from OS was slower with 23% lower Cmax compared to tablet.

PopPK analysis was conducted to simulate the PK profiles under multiple-dose, steady state conditions and the concentrations profiles changes during the switches between those largest change in PK parameters among all the scenarios, the tablet formulation administered under fasted state and the OS formulation given under fed condition. A population PK model was developed based on Study 048 data alone which captured the PK data reasonably well.

Based on popPK simulated multiple-dosing scenario at steady state, the AUC and also Cmax of perampanel were BE between treatments (i.e., before and after switching from one formulation/food intake status to another formulation/food intake status). Therefore, the difference in Cmax observed in the single-dose evaluation is not considered to be clinically meaningful. In conclusion, the oral suspension formulation demonstrated comparable bioavailability as the tablet formulation and can be used interchangeably.

The pivotal PK study was audited and Office of Study Integrity and Surveillance (OSIS) concluded that the clinical and analytical portions of the Study E2007-A001-048 are acceptable.
In summary, Drs. Yang, Krudys and Men reviewed the submission and the team concluded that NDA 208277 is approval from an OCP perspective.

5. Efficacy

There is no clinical efficacy trial conducted.

6. Safety

Safety data from the pivotal PK study E2007-A001-048 and a pilot relative bioavailability (BA) study (Study E2007-E044-028) were reviewed by Drs. Getzoff and Hershkowitz. Both of them agree that there are no clinical safety issues impeding the approval of the proposed product.

There is only one additional safety matter noted that is requiring a labeling change in section 5.1 regarding the collected reports of psychosis (acute psychosis, hallucinations, delusions, paranoia) and delirium (delirium, confusional state, disorientation, memory impairment) in patients treated with perampanel.

In summary, from a clinical perspective, there is no obvious new safety signals were observed. It is therefore recommended approval.

7. Advisory Committee Meeting

None

8. Pediatrics

Pediatric Review Committee (PeRC) meeting was held on February 24, 2016. It is agreed that Fycompa had been fully assessed for pediatric patients 12 years of age and older for the POS and PGTC indications and on the plan for waivers and deferrals for the younger pediatric populations, including the plan for full extrapolation of efficacy for pediatric patients 4 years of age and older with POS with new extrapolation policy issued in November, 2015.

The Agency will only request an open safety study, which is a new PMR listed below:

A long-term, open-label, safety study of adjunctive therapy in patients 1 month to < 12 years with epilepsy. The purpose of this study is to evaluate the long-term safety of perampanel as adjunctive therapy in the treatment of partial-onset seizures (ages 1 month to < 12 years) or primary generalized tonic-clonic seizures in pediatric patients (ages 2 to < 12 years). Doses for this study must be at or above those doses determined to be efficacious by Study 1932-4 (patients 1 month to < 4 years old with partial-onset seizures), Study 2922-1 (patients 2 to < 12 years with primary generalized tonic-clonic seizures), and the pharmacokinetic analyses used for the extrapolation of efficacy in pediatric patients 4 to < 12 years with partial-onset seizures. This study may include
subjects enrolled in the extension phases of Studies 1932-1, 1932-2, 1932-4, and 2922-1, and may be supplemented as necessary. A minimum of 100 patients must be exposed to study drug for one year at or above the dose or doses identified as effective. Subjects should be balanced among age cohorts to allow for adequate conclusions to be drawn.

There were no changes to the Pediatric Use section of labeling as a result of this application.

9. Financial disclosures:

There is no financial arrangement introduced significant bias into the results of the pivotal 048 PK trial.

10. Labeling

See labeling included in the Divisions action letter. Please note that due to the Pregnancy and Lactation Labeling Rule (PLLR) took effect on June 30, 2015, the recommendations are consistent with the PLLR format.

11. Recommended Regulatory Action

The Sponsor’s submission provides adequate information for regulatory approval.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUXIN MEN
04/29/2016