

Clinical Pharmacology Review

PRODUCT (Generic Name):	Perampanel
PRODUCT (Brand Name):	FYCOMPA®
sNDA:	202-834/s-012; 208-277/s-001
DOSAGE FORM:	Tablet and Suspension
ROUTE of ADMINISTRATION:	Oral
INDICATION:	Monotherapy for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older
SUBMISSION DATE:	9/26/2016
SPONSOR:	Eisai Co.
Clinical Pharmacology REVIEWER:	Dawei Li, Ph.D.
TEAM LEADER:	Kevin Krudys, Ph.D. (Pharmacometrics) Angela Men, M.D., Ph.D.
OCP DIVISION:	DPM/DCP I

1 BACKGROUND

Perampanel is an orally active, noncompetitive, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. It was approved in the U.S. as adjunctive therapy for the treatment of POS with or without secondarily generalized seizures and primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older. There are different dosing recommendations based on the presence or absence of enzyme-inducing antiepileptic drugs (EIAEDs). In this supplemental application, the sponsor is seeking the approval of perampanel as monotherapy for the treatment of POS in patients with epilepsy aged 12 years and older based on extrapolation of the efficacy and safety of perampanel in adjunctive therapy for the treatment of POS. The sponsor proposes the same titration and dosage in monotherapy as the previously approved language for adjunctive POS in the absence of EIAEDs:

- Starting dose: 2 mg once daily orally at bedtime.
- May increase dose based on clinical response and tolerability by increments of 2 mg once daily no more frequently than at weekly intervals.
- Recommended maintenance dose in monotherapy for partial-onset seizures: 8 mg to 12 mg once daily at bedtime.
- Individual dosing should be adjusted based on clinical response and tolerability.

- Measure oral suspension using provided adaptor and dosing syringe

2 GENERAL ADVICE FOR MONOTHERAPY EXTRAPOLATION

On September 13, 2016 DNP sent a General Advice Letter to the Sponsor indicating that it was acceptable to extrapolate the efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS.

To support use as monotherapy for the treatment of POS based on extrapolation, a Sponsor must provide pharmacokinetic information adequate to demonstrate that the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

3 RESULTS OF SPONSOR'S ANALYSIS

The Sponsor relied on population PK (Report CPMS-E2007-2011-002) and PK/PD (Report CPMS-E2007-2011-003) analyses to support monotherapy dosing. These reports were submitted with the original POS NDA and reviewed previously (DARRTS 10/19/2012). Briefly, CPMS-E2007-2011-002 was conducted to characterize the PK profile of perampanel in healthy subjects from 19 Phase 1 studies. The PK population consisted of 606 subjects, receiving single doses of perampanel (0.2 mg to 36 mg) or repeated perampanel dosing for up to 21 days (1 mg to 12 mg QD). CPMS-E2007-2011-003 is a PK and PK/PD analysis of pooled data obtained in the three pivotal Phase 3 studies conducted in 770 patients with POS (Studies 304, 305, and 306). The objectives of the analyses were to describe the PK of perampanel given as adjunctive therapy in epileptic patients with POS, to describe the exposure-response relationship between the exposure to perampanel and efficacy and to assess potential interactions with concomitant AEDs. Key conclusions of these analyses, as documented in the previous clinical pharmacology review (DARRTS 10/19/2012) include the following:

- Clearance (CL/F) of perampanel in patients not on EIAEDs was estimated as 0.73 L/hr or 0.605 L/hr for males and females, respectively. These estimates were similar to the CL/F (0.652 L/hr) estimated for healthy subjects.
- In the presence of EIAEDs the exposure of perampanel was decreased by approximately 50-67%

These findings support the conclusion that perampanel PK in POS patients receiving adjunctive therapy without concomitant EIAEDs should be similar to that in patients treated with perampanel monotherapy. Therefore, the Sponsor's proposed perampanel dosing regimen for monotherapy (same as perampanel adjunctive therapy for POS in the absence of EIAEDs) should yield similar exposure in POS patients compared to perampanel adjunctive therapy without concomitant EIAEDs.

The Sponsor also reported the results of a PK/PD analysis that showed no effect of sex, age, race, or co-administration of any AED on the slope of the plasma exposure-response relationship, implying that there were no PD interactions between any AED and perampanel. A similar analysis performed by Dr. Lee during the original review

(DARRTS 10/19/2012) confirmed the lack of a pharmacodynamic interaction. Although these analyses may lend support to the concept of extrapolation from adjunctive therapy to monotherapy they are not necessary to derive monotherapy dosing recommendations for this application.

4 SUMMARY

Perampanel PK in POS patients receiving adjunctive therapy without concomitant EIAEDs is expected to be similar to that in patients treated with perampanel monotherapy. Therefore, the Sponsor's proposed perampanel dosing regimen for monotherapy (same as perampanel adjunctive therapy for POS in the absence of EIAEDs) is acceptable.

5 RECOMMENDATIONS

The Office of Clinical Pharmacology reviewers have reviewed the submission and find NDA 202-834/s012, 208-277/s-001 acceptable from Clinical Pharmacology's perspective provided that an agreement is reached between the Sponsor and the Agency regarding the recommended labeling language.

Dawei Li, Ph.D.

Reviewer, Division of Clinical Pharmacology 1 (DCP1)

Kevin Krudys, Ph.D.

Team Leader, DPM

Concurrence:

Angela Men, M.D., Ph.D. _____

Team Leader, DCP1

cc: HFD-120 NDA # 202-834/s-012; 208-277/s-001
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Dawei Li

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/s/

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