Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Perampanel

Proprietary Product Name: Fycompa

Sponsor: Eisai Australia Pty Ltd

October 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
A_e	amount of drug excreted in the urine
AED	antiepileptic drug
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMS	accelerator mass spectrometry
BCRP	breast cancer resistance protein
CBZ	carbamazepine
CRT	Choice Reaction Test
CTT	Continuous Tracking Test
DB	double blind
df	degrees of freedom
E2007	perampanel
FBM	fat body mass
hERG	human ether-a-go-go related gene
HSA	human serum albumin
IC_{50}	concentration of half-maximal inhibition
IEC	Independent Ethics Committee
IIV	inter-individual variability
ΔIIV	change in IIV
IOV	inter-occasion variability
IRB	Institutional Review Board
IVRS	interactive voice recognition system
KSS	Karolinska Sleepiness Scale
MTD	maximum tolerated dose
NRU	neutral red uptake

Abbreviation	Meaning
OATP	organic anion transporting polypeptides
OFV	objective function value
ΔOFV	change in OFV
OL	open label
OLE	Open-label Extension
PI	phototoxic index or prediction interval
PSV	peak saccadic velocity
PTF	peak-trough fluctuations
R_{ac}	accumulation ratio
STM	Sternberg Short Term Memory Scanning Task
V_d/F	apparent volume of distribution
VAMS	Bond and Lader Visual Analog Mood Scale

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	16 May 2014
Active ingredient:	Perampanel (as hemisesquihydrate)
Product name:	Fycompa
Sponsor's name and address:	Eisai Australia Pty Ltd Eisai Australia Pty Ltd/Commercial Eyes Pty Ltd 651 Victoria Street Abbotsford, VIC 3067
Dose form:	Film-coated tablets
Strengths:	2 mg, 4 mg, 6 mg, 8mg, 10 mg and 12 mg
Container:	Blister pack
Pack sizes:	7s (2 mg) and 28s (4, 6, 8, 10 and 12 mg)
Approved therapeutic use:	*Fycompa is indicated for the adjunctive treatment of partial-onset seizures with or Without secondary generalised seizures patients with epilepsy aged12 years and older.*
Route of administration:	Oral (PO)
Dosage:	Fycompa must be titrated, according to individual patient response, in order to optimise the balance between efficacy and to 16rability. Perampanel should be taken orally once daily before bedtime. Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in partial-onset seizures. Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and to16rability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day.
ARTG number:	207691

Product background

This AusPAR describes the application by the sponsor Eisai Australia Pty Ltd to register a new chemical entity, perampanel (as Fycompa). Fycompa is a first in its class of selective

non-competitive antagonist of the ionotropic AMPA[1] glutamate receptor on post-synaptic neurons. It has been proposed for adjunctive treatment of partial-onset seizures with the following indications:

> *Fycompa is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in epileptic patients aged ≥12 years, with treatment initiated at 2 mg/day and increased based on clinical response/tolerability.*

Epilepsy is characterised by seizures, which are episodes of abnormal, synchronous neuronal firing usually accompanied by a reduction in awareness or by focal neurological symptoms. Seizures are usually classified into focal ('partial') seizures, which begin in one part of the brain, or primary generalised seizures, which involve the whole brain network from the onset of the seizure. Focal seizures may spread, eventually involving the whole brain as the seizure progresses and these are known as secondarily generalised seizures. Focal seizures are the most common form of seizures, though the seizures may spread so rapidly that the initial focal phase is not clinically apparent.

Antiepileptic drugs (AEDs) can often reduce the frequency and severity of seizures, producing lasting seizure-free intervals in some patients but up to 30% of patients with epilepsy are resistant to drug treatment and continue to have frequent seizures despite treatment. Most existing anticonvulsants work by inhibiting sodium channels, by enhancing or mimicking the inhibition mediated by endogenous gamma-amino butyric acid (GABA) or by inhibiting the release of excitatory neurotransmitters. Inhibiting voltage-gated calcium channels can also be useful for some seizure types.

Regulatory status

This is an application for a new chemical entity for Australian regulatory purposes.

Perampanel was approved for the indication proposed by the sponsor in the USA in 2012 (see Table 1). It was determined to be a Class III controlled substance in the USA. Perampanel is also approved for the proposed indication in the European Union (EU) where it is scheduled as a prescription only product. The product has also been approved by Health Canada.

Table 1. International regulatory status

Country	Approval Date	Approved Indication
European Union* (Centralised Procedure)	23/07/2012	**Fycompa** is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.
United States	21/10/2012	**Fycompa**, a non-competitive AMPA glutamate receptor antagonist, is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older
Switzerland	17/12/2012	**Fycompa** is indicated for the adjunctive treatment of partial-onset (focal) seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older.
Canada	04/04/2013	**Fycompa** (perampanel) is indicated as adjunctive therapy in the management of partial-onset seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy. Geriatrics (>65 years of age) There is limited information on the use of FYCOMPA in subjects over 65 years of age. Pediatrics (< 18 years of age) The safety and efficacy of FYCOMPA in pediatric patients has not been established and its use in this population in not indicated.

[1] The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor is a non-N-methyl-D-aspartate receptor (NMDA; glutamate gated cation channels with high calcium permeability) type ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the central nervous system.

Product Information

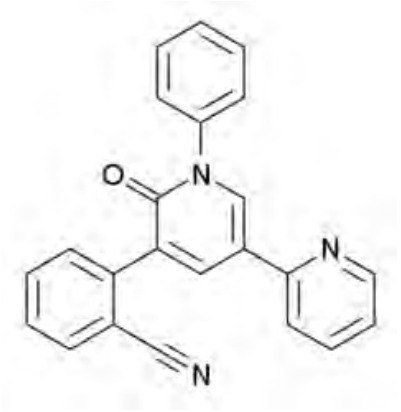
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

Drug substance (active ingredient)

Perampanel, a substituted bipyridine derivative (see structure in Figure 1 below), is a selective non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over excitation. The precise mechanism by which Fycompa exerts its antiepileptic effects has not been fully elucidated.

Figure 1. Chemical structure of perampanel



Perampanel exists in several polymorphic forms. One hydrate (the hemisesquihydrate) and several anhydrous forms are known.

The PI states Fycompa may be taken with or without food (at bedtime).

There are no British Pharmacopiea (BP) or US Pharmacopeia (USP) monographs for the active pharmaceutical ingredient (API) or the finished product. Perampanel hemisesquihydrate[2] has been accepted as an Australian Approved Name (AAN).

The two starting materials are obtained commercially. A detailed justification for the appropriateness of these materials as starting materials has been provided.

Drug product

The proposed products are immediate-release film-coated tablets containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg perampanel (as hemisesquihydrate).[3]

The tablets are film-coated to differentiate the various strengths and to prevent discolouration of the perampanel core (the results of the photostability study refer).

The proposed excipients are all conventional substances with well-known properties and functions and commonly used as ingredients in this type of medicine. There are no obvious

[2] 'modified USAN to include water of hydration'.
[3] As previously discussed, confirmation is required.

compatibility problems with the formulation and none were observed in compatibility studies.

Thus, two formulations are proposed for marketing: Formulation C (2 mg and 4 mg film-coated tablets) and Formulation D (6 mg, 8 mg, 10 mg, and 12 mg film-coated tablets).

The form of the API, the formulation and the manufacturing processes have been adequately justified, logically developed and optimised with reference to the physical, chemical and pharmacological properties and compatibilities of the API and excipients, the dose form, uniformity of dose delivery and the intended clinical use of the products.

Control of drug product

The proposed specifications are acceptable.

Stability

A shelf-life of 4 years when stored below 30°C for the 2 mg and 4 mg tablets and 3 years[4] when stored below 30°C for the 6 mg, 8 mg, 10 mg and 12 mg tablets is supported by the data provided.

Dose proportionality

The sponsor has provided the results of Bioequivalence Study E207-E044-016, designed to demonstrate bioequivalence between two of the proposed 2 mg tablets and the proposed 4 mg tablet and Bioequivalence Study E2007-E044-037, designed to demonstrate bioequivalence between six of the proposed 2 mg tablets and the proposed 12 mg tablet. These studies are discussed under *Biopharmaceutics* below.

Biopharmaceutics

The bioavailability and bioequivalence studies are briefly summarised below. The pivotal bioavailability/bioequivalence studies have been evaluated in full.

Clinical and commercial formulations

Several formulations were investigated during the development phase:

- Formulation A (perampanel 0.1, 1, and 5 mg film-coated tablets) was developed to initiate clinical studies and used in the early stage of clinical studies (predominantly Phase I studies).
- Formulation A was re-formulated to Formulation B. Formulation B (perampanel 0.25, 0.5, 1, and 2 mg film-coated tablets) was used predominantly in Phase II studies. A Bioequivalence Study (E2007-A001-008) was conducted to establish bioequivalence between the two formulations.
- Formulation C (perampanel 1, 2, and 4 mg film-coated tablets) was developed to manufacture tablets distinguishable among the strengths used in the clinical study by changing the colour of the perampanel 2 mg film-coated tablet from yellow (Formulation B) to orange (Formulation C) and by manufacturing a perampanel 4 mg film-coated tablet with a different colour (red) and size. Formulation C (1, 2, and 4 mg tablets) was used during the final stage of clinical studies (that is, E2007-E044-301,

[4] See Appendix A of Note for guidance on evaluation of stability data, <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002649.pdf>

E2007-A001-302, E2007-G000-304, E2007-G000-305, E2007-G000-306, and E2007-G000-309).

- In addition to Formulation C (perampanel 1, 2, and 4 mg film-coated tablets), Formulation D (perampanel 6, 8, 10, and 12 mg film-coated tablets) was developed as a commercial formulation (Formulations C and D are similar). The perampanel 6 and 12 mg film-coated tablets (Formulation D) were compared to the perampanel 2 mg film-coated tablet in Bioequivalence Studies E2007-E044-037, E2007-A001-039 and E2007-A001-040.

Thus, two formulations are proposed for marketing: Formulation C (2 mg and 4 mg film-coated tablets) and Formulation D (6 mg, 8 mg, 10 mg, and 12 mg film-coated tablets).

Biopharmaceutic study overview

The supporting biopharmaceutic studies relating to bioavailability, bioequivalence and food effect are summarised in the table below.

Table 2. Summary of Biopharmaceutic Studies: Overview of study designs and results

Study No.	Study Design and Objective	Treatments	Subjects	Results/Conclusions
Absolute BA, Relative BA, and Absorption Studies				
E2007-E044-017	Open-label study to determine absolute oral BA and investigate metabolite profile	i.v. solution of ^{14}C-perampanel (10 µg/200 nCi) + oral dose of perampanel 8 mg (2 × 4-mg tablets, Formulation C)	10 healthy males age range, 22 –53 y	Due to analytical problems, only five of ten subjects provided concentration-time profile of unchanged ^{14}C-perampanel. Using these data, the estimated mean (SD) absolute bioavailability was 116% (9.4%).
E2007-E044-028	Open-label, two-period, two-sequence crossover study to determine the relative BA of two oral formulations	4-mg oral perampanel tablet (Formulation C) 4 mg dose of perampanel oral suspension	16 healthy adults (9 males/7 females) age range, 20 – 53 y	The oral suspension and the tablet had similar bioavailability in terms of extent of exposure as measured by $AUC_{(0-72)}$ and $AUC_{(0-\infty)}$. However, the rate of absorption for the suspension was slower than that of the tablet as shown by a prolonged t_{max} and an associated reduction in C_{max} compared with the tablet formulation.
E2007-E044-007	Open-label study to obtain information on the absorption, metabolism, and elimination of ^{14}C-perampanel	2-mg oral tablet (Formulation B) to which was applied a ^{14}C-perampanel solution (200 nCi)	8 healthy elderly adults (4 males/4 females) age range, 65 – 79 y	Mean recovery of ^{14}C-radioactivity = 70.1%, with approximately 70% excreted in the feces and 30% in the urine. No parent drug recovered in the feces; thus, perampanel appeared to be completely absorbed following oral administration. PK profile of ^{14}C-perampanel was similar to that of the parent compound: both radiolabeled and unlabeled perampanel were rapidly absorbed, with average maximum plasma concentrations achieved within the first hour after drug administration. The median $t_{1/2}$ of ^{14}C was longer and the total exposure (AUC) slightly greater than the respective values for perampanel.
E2007-A001-008	Open-label, randomized, two-period, two-sequence crossover study to evaluate BE of two oral tablet formulations	2 × 1-mg oral tablet (Formulation A; reference) 2 × 1-mg oral tablet (Formulation B; test)	34 healthy adults (23 males/11 females) age range, 18 – 45 y	2 mg oral doses (2 × 1 mg tablets) of the test (Formulation B) and reference (Formulation A) tablets were bioequivalent when administered to healthy men and women
E2007-E044-016	Open-label, randomized, crossover study to establish dose strength equivalence	2 × 2-mg oral tablets (Formulation C) 1 × 4-mg oral tablet (Formulation C)	24 healthy adults (12 males/12 females) age range, 20 – 55 y	BE demonstrated for the two dose strengths based on rate and extent of exposure
E2007-E044-037	Open-label, two-period, two-sequence crossover study to evaluate BE between oral tablet Formulations C and D	6 × 2-mg oral tablets (Formulation C) 1 × 12-mg oral tablet (Formulation D)	28 healthy adults (21 males/7 females) age range, 21 – 54 y	The geometric means ratio (90% CI) of $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max} of the 12 mg tablet to 6 × 2-mg tablets was 99.2% (94.4%, 104%), 102% (92.8%, 111%), and 86.4% (78.4%, 95.3%), respectively. Thus, $AUC_{(0-t)}$ was within the BE criteria of 80% to 125%, but C_{max} slightly deviated from the criteria. Therefore, BE of the two formulations could not be concluded.
Study No.	**Study Design and Objective**	**Treatments**	**Subjects**	**Results/Conclusions**
BE Studies (continued)				
E2007-A001-039	Open-label, two-period, two-sequence crossover study to evaluate BE between oral tablet Formulations C and D	3 × 2-mg oral tablets (Formulation C) 1 × 6-mg oral tablet (Formulation D)	54 healthy adults (34 males/20 females) age range, 18 – 55 y	Based on rate and extent of exposure, BE was demonstrated for one 6-mg tablet of Formulation D and 3 × 2-mg tablets of Formulation C.
E2007-A001-040	Open-label, two-period, two-sequence crossover study to evaluate BE between oral tablet Formulations C and D	6 × 2-mg oral tablets (Formulation C) 1 × 12-mg oral tablet (Formulation D)	54 healthy adults (32 males/22 females) age range, 18 – 54 y	Based on rate and extent of exposure, BE was demonstrated for one 12-mg tablet of Formulation D and 6 × 2-mg tablets of Formulation C.
Food Effect Studies				
E2007-E044-003	Open-label, randomized, single-dose, two-way crossover study to evaluate the effect of food on PK and PD	1-mg oral tablet (Formulation A); fasting 1-mg oral tablet (Formulation A); fed	24 healthy adults (12 males/12 females) age range, 19 – 41 y	Rate, but not extent of exposure decreased when perampanel was administered following a high-fat breakfast vs. after an overnight fast. Measures of the magnitude of sedation, in particular decreases in peak saccadic velocity, tended to parallel plasma perampanel concentrations.
E2007-E044-009	Single-dose, randomized, active, and placebo-controlled parallel group, double-blind, double-dummy study to evaluate the impact of food on PK and PD[a]	6 mg perampanel (3 × 2-mg oral tablets, Formulation B); fasting 6 mg perampanel (3 × 2-mg oral tablets, Formulation B); fed Oral placebo; fasting or fed Oral diazepam 5 mg; fasting	8 healthy adults (7 males/1 female) 8 healthy adults (7 males/1 female) 8 healthy adults (6 males/2 females) 7 healthy adults (6 males/1 female) age range, 18 – 55 y	Peak perampanel exposure (C_{max}) was 28% lower and occurred 3 h later (t_{max}) when a 6 mg dose was given with a high-fat meal vs. after an overnight fast. The extent of perampanel exposure ($AUC_{(0-24)}$) showed no noteworthy difference in the fed vs. fasted subjects. Consistent with the PK findings, administration of perampanel with food vs. in the fasting condition delayed the onset but did not alter the extent of sedation.

AUC = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration ($AUC_{(0-t)}$) or extrapolated to infinity ($AUC_{(0-\infty)}$), BA = bioavailability, BE = bioequivalence, CI = confidence interval, C_{max} = maximum plasma concentration, i.v. = intravenous, PD = pharmacodynamics, PK = pharmacokinetics, SD = standard deviation, $t_{1/2}$ = terminal elimination half-life

a. Only the single-dose phase of this dose-finding study examined the effect of food on PK and PD. Complete results for the single- and multiple-dose study phases are presented in 2.7.2.2.2.

Study E2007-E044-017: The dossier notes that the rationale for absolute bioavailability above 100% is not clear but suggests that variability in the AMS derived pharmacokinetic data for the IV dose and the LC/MS data for the oral dose may have contributed to overestimation. In any case, the estimated absolute bioavailability indicates that absorption of perampanel is essentially complete.

Conclusion

Provided that some issues identified by the evaluator are resolved, the proposed 12 mg tablets (Formulation D) can be considered bioequivalent to 6x2 mg tablets (Formulation C).

Justification submitted for non-supply of bioavailability/bioequivalence data

A justification for not submitting bioequivalence studies for the proposed 8 mg and 10 mg tablets has been provided. It addresses the requirements of Section 4 of Appendix 15 of the ARGPM and nonclinical aspects of the justification were considered.

The company has also considered the conditions set out in section 4.1.6 of TGA adopted EU guidance '*Guideline on the Investigation of Bioequivalence*'.

The justification is acceptable from a pharmaceutical chemistry perspective.

Quality summary and conclusions

The submission and the supporting data relating to the composition, development, manufacture, quality control and stability as well as the biopharmaceutic aspects of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Recommendation

Although a number of significant deficiencies were identified in the submission during the initial assessment, approval was eventually recommended from a quality/biopharmaceutics perspective.

III. Nonclinical findings

Introduction

The general quality of the submitted studies was high and comprehensive. Pivotal studies examined the repeat dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity of perampanel, with most studies conducted under Good Laboratory Practice (GLP) conditions. Most of the safety related studies submitted were also conducted under GLP conditions or in established laboratories and adequately documented.

Pharmacology

Primary pharmacology

Submitted in vitro sponsor and published studies investigated the effects of perampanel and its metabolites on cultured rat cortical neurons. Results showed that perampanel potently inhibits the AMPA induced increase in intracellular free calcium (Ca^{2+}) concentration, with minimal effect on NMDA induced increases. The perampanel metabolites examined had weaker antagonistic effects on AMPA-type glutamate receptor compared to the parent drug.

Eighteen in vivo studies of various disease state models in mice, rats and primates were submitted. Perampanel treatment in AMPA induced seizure models in mice indicated a dose-dependent prolongation of seizure latency suggesting perampanel is an orally active, non-competitive, selective AMPA receptor antagonist. Perampanel appeared to protect

mice from anticonvulsant activity such as generalized tonic-clonic seizures in an audiogenic seizure model and a maximal electroshock seizure model as well as protecting mice from myoclonic seizures in the pentylenetetrazol-induced seizure model. Perampanel dose-dependently delayed or abolished kindling development in the kindling model but was not effective in the GAERS model[5]. Perampanel was shown to dose-dependently increase the paw-withdrawal threshold in animal models of neuropathic pain as well as decrease disease scores without affecting either peripheral antibody production or central nervous system (CNS) perivascular cuffing in Experimental Autoimmune Encephalomyelitis (EAE) rodent models. Finally, perampanel was shown to enhance the effect of L-3,4-dihydroxyphenylalanine (L-DOPA) in primate animal models of Parkinson's disease.

The results of the nonclinical primary pharmacology studies are supportive for the proposed indication.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic studies tested perampanel against a panel of 63 receptors, enzymes and other targets in vitro. Results showed no significant binding (>50% inhibition), suggesting perampanel may be a highly selective agent that inhibits AMPA-type glutamine receptor activity by a non-competitive mechanism with no significant affinity for unrelated physiological targets in the cell. Perampanel (1, 10 µg/mL) had no significant binding in vitro (>50% inhibition) to any of the 86 receptor channel and transporter targets with weak binding observed at the melatonin 1 receptor (MT1) (h) receptor (1 µg/mL), as well as adenosine receptors 1 (A1) (h), 2A (A2A) (h), 3 (A3) (h), benzodiazepine receptor (BZDc), gamma-aminobutyric acid receptor A (GABAA), MT1(h), melatonin post-junctional receptor (ML2) melatonin type 3 receptor (MT3), M1, k opioid receptor (KOP) and serotonin 1A receptor (5-HT1A) (h) receptors (10 µg/mL). When perampanel was tested against a panel of 8 cytokine secretion assays and 1 immunosuppression assay it was found that the 50% inhibitory concentration (IC_{50}) for each of the reference compounds was within accepted limits of historic average ± 0.5 log units. Submitted studies evaluating motor coordination in mice and rats found that perampanel dose-dependently decreased motor coordination with the 50% effective concentration (ED_{50}) at 1.8 mg/kg in mice and 9.14 mg/kg in rats, with most doses tested impairing motor coordination.

Submitted CNS studies evaluated daily oral (PO) administration of perampanel to rats. There were slight, but reversible, decreases in alertness, spontaneous activity, touch response, body position, limb tone, grip strength, body and abdominal tone, staggering gait and inhibition of palpebral opening observed at 5 mg/kg with no adverse effects at lower doses. Perampanel had no effects on body temperature up to 5 mg/kg in rats. Effects on the cardiovascular system were assessed in a dog study in vivo and in a potassium channel (hERG) assay in transfected hamster embryonic kidney (HEK293) cells in vitro. The hERG study found that perampanel inhibited hERG tail currents at ≥10 µmol/L, with the IC_{50} 15.8 µmol/L (5.5 µg/mL). This IC_{50} is about 7.5 times the anticipated mean clinical peak plasma concentration (C_{max}) (720 ng/mL; see *Relative exposure* below); the no-effect concentration was 3 µmol/L (approximately 1.5 times C_{max}). When adjusted for plasma protein binding (approximately 95.5%; see *Pharmacokinetics* below), the IC_{50} and No Observable Effect Level (NOEL) concentrations are about 170 times and 30 times, respectively, the mean clinical plasma C_{max} (free fraction) of 32.4 ng/mL. When administered once orally to dogs (1, 10 mg/kg) perampanel was found to have no adverse effects on heart rate, mean blood pressure or electrocardiogram (ECG) parameters which

[5] Genetic Absence Epilepsy Rats from Strasbourg (GAERS), an inbred strain of Wistar rats with absence epilepsy.

suggests that perampanel has a relatively low potential to cause QT prolongation[6]. Plasma concentrations were not measured in this study but the 7 day and 4 week dog studies noted a plasma C_{max} following the first 10 mg/kg PO dose of approximately 225 ng/mL (that is, well below the clinical C_{max} value, although toxicity would have limited testing of higher doses). The available data indicate that perampanel has a weak effect on hERG currents in vitro at high concentrations but no effect at clinical plasma concentrations.

The results of the other safety pharmacology studies were unremarkable and consistent with the pharmacological activity of perampanel.

The available data suggest that perampanel is a potent, non-competitive AMPA-type glutamate receptor antagonist which doesn't bind to the other excitatory amino acid receptors (NMDA and kainate) or to a number of other receptors and transporters. Safety pharmacology studies have not identified risks of serious adverse effects on the CNS, cardiovascular or respiratory systems. Similar CNS depressant effects have also been observed with other anticonvulsants and AMPA antagonists.

Pharmacokinetics

The results from the submitted studies in rats, dogs and monkeys indicate that perampanel has a low to moderate clearance and a moderate to large volume of distribution, with no accumulation observed after repeated dosing in mice, rats, dogs and monkeys. In all species tested and at high doses, systemic exposure after repeated dosing increased in less than a dose-proportional manner. In single dose studies clearance was greatest in rats (1239 mL/h/kg), followed by dogs (780 mL/h/kg) and monkeys (185 mL/h/kg). The oral clearance from human plasma/blood is approximately 15/30 mL/min, substantially lower than hepatic blood flow (1500 mL/min). The terminal half-life was very much shorter in the tested species (1.4, 6.9, 6.9 h in rats, dogs, monkeys, respectively) compared to humans (105 h). The only gender difference in systemic exposure was noted in rats (female > male).

In distribution studies with radioactively labelled (^{14}C)-perampanel, radioactivity was widely distributed in various tissues (especially liver > adipose tissue > adrenal) and, with the exception of the aorta and pigmented tissues in rats (eyeball) and Cynomolgus monkeys (ocular tissues), eliminated rapidly from tissues. In Sprague Dawley (SD) rats, highest levels of radioactivity at 1 and 3 weeks post dose were found in the aorta, and in pigmented rats the respective half-lives of radioactivity in aorta and eyeball were 110 and 45 weeks. The extended residence time in the eyeball of rats (pigmented > albino), and also monkeys, suggests binding of perampanel and/or perampanel related material to melanin. The very long residence time in aorta is suggestive of a covalent interaction with a component of the aorta, possibly elastin. No histopathologic findings in the vasculature and eyes were observed in either species in the toxicity studies, suggesting that accumulation of perampanel derived material in these tissues may not have toxicologic consequences. However, an ultrastructural analysis of the aorta has not been conducted following perampanel treatment and other compounds which accumulate in aorta have been associated with adverse cardiovascular effects (for example, rofecoxib).

In pregnant female rats, ^{14}C-perampanel radioactivity was distributed to the fetus (although amounts were low; ≤0.09% of the dose administered), indicating that perampanel and/or its metabolites cross the placenta. Levels in fetal blood, brain, heart, lung, liver and kidney were within the range of 10 to 60% of maternal levels. Studies with

[6] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death.

^{14}C-perampanel radioactivity also found that perampanel and/or its metabolites were excreted into the milk in lactating rats (milk/plasma ratio 3 to 4).

Plasma protein binding of perampanel was high and broadly similar in mice, rats, dogs, monkeys and humans: 94%, 87%, 90%, 91% and 95.5% respectively at 200 ng/mL (the tested concentration most relevant to clinical plasma levels).

There were limited investigations of perampanel metabolism; studies showed a qualitatively similar metabolic profile in test species and humans, with no metabolites specific to humans reported. The major drug related component in plasma was unchanged perampanel in rats, monkeys and humans. Metabolism of perampanel was investigated in both in vivo and in vitro studies. In rats, three metabolites were recovered in excreta: M1 (ER-179392-00, 4'-OH-perampanel), M12 (the glucuronide of M1), and M2 (ER-260862-00, a carboxylic acid metabolite). M1 and M12 represented approximately 35% of the dose excreted in urine and faeces (M1 26%, M12 8%), and M2 about 15% of the dose. The predominant material in plasma and cerebrum at 1 h postdose was unchanged perampanel. In monkeys, no major metabolites were found in plasma (up to 48 h), but excreta was reported to contain M1, M2, M12 and M13 (each 3-6% of the dose). In dog liver microsomes, the two metabolites detected were DM1 (M6, an intermediate in M2 formation) and DM2 (M1). In mouse, rat, monkey and human liver microsomes or cryopreserved hepatocytes, a qualitatively similar profile of metabolites was observed, with up to 16 metabolites (M1-16) reported, with broad overlap across species. The profile suggested initial oxidation at the pyridine, benzene or benzonitrile ring followed by glucuronidation. No human-specific metabolites were detected. As discussed above (*Primary pharmacology*), some metabolites had pharmacological activity but were much less potent than perampanel.

Cytochrome P450 enzyme (CYP450) studies with recombinant human CYPs, anti-human CYP3A4 antibody and ketoconazole revealed CYP3A4 and/or CYP3A5 as the primary isoforms underling the primary oxidative metabolism of perampanel. In induction and inhibition studies in vitro, perampanel elicited relatively weak induction of CYP3A4/5 and even less induction of CYP2B6 in cultured human hepatocytes; there was no convincing evidence for induction of CYP1A2 or glucuronosyltransferases (UGTs). In human liver microsomes, perampanel inhibited CYP2C8 and UGT1A9 at a high concentration (30 µmol/L, approximately 15 times clinical C_{max}) but not other CYP and UGT isoforms. In transporter studies, perampanel was a weak inhibitor of organic anion transporter 1 (OAT1), OAT3, OCT1, P-glycoprotein 1 (P-gp; permeability glycoprotein) and Breast Cancer Resistance Protein (BCRP) only, and was not a substrate for several transporters tested.

The combined available information on interactions of perampanel with CYP isozymes and transporters suggests minimal potential for interactions with other medicines at usual clinical exposures.

Excretion of perampanel related material was predominantly via the faecal route in rats (88% versus 12% via urine) and monkeys (57% versus 37% via urine).

Toxicology

Single dose toxicity

Six single dose PO toxicity studies in mice, rats, rabbits, dogs and monkeys reported no deaths at doses up to 1500 (mice), 1000 (rats; 2000 lethal in females), 300 (rabbits), 10 (dogs) and 4 mg/kg (monkeys). In rodents the clinical signs included pharmacology-based CNS effects consisting of abnormal gait, hypoactivity, prostration, dyspnea (mice only), bradypnea and hypothermia (rats only) as well as mydriasis (rats only). A similar

constellation of pharmacology based CNS clinical signs such as ataxia and prostration were observed in rabbits, dogs and monkeys.

Repeat dose toxicity

Sixteen repeat dose studies were submitted, conducted in mice, rats, dogs and monkeys. The common theme apparent in the repeat dose studies in all tested species was the occurrence of clinical signs. Mice studies found perampanel to be lethal at ≥ 60 mg/kg with observed severe clinical signs consisting of abnormal gait, decreased activity, prostration and dyspnea and also skin lesions such as loss of digits or excoriation of the skin or prolapse/trauma of the penis. A 13 week study in female mice found a dose-dependent decrease in corpus luteum at ≥100 mg/kg. Rat studies reported perampanel related deaths in males at 100 to 300 mg/kg and in females at 30 mg/kg with treatment causing dose related CNS related clinical signs such as abnormal gait, decreased activity, and prostration which became less severe upon repeated administration. The maximum tolerated dose (MTD) in rats by oral repeat dose was 100 mg/kg in males and 30 mg/kg in females. Dog studies found no drug related mortality at ≤10 mg/kg and toxicity was limited to clinical signs, abnormal gait (≥ 1 mg/kg) and vomiting (10 mg/kg). No drug related toxicity in clinical pathology and histopathology was noted at any dose up to 13 weeks of dosing. Following perampanel treatment in Cynomolgus monkey, ataxic gait was observed in the males and females at ≥ 0.3 mg/kg and CNS clinical signs other than ataxia consisting of decreased spontaneous activity, sitting position, and transient prostration (1 mg/kg). A 39 week repeat dose monkey study showed severe adverse clinical signs such as sedative behaviours consisting of somnolence, coma, sitting position, lateral position, and prone position (8 mg/kg).

Combination toxicity studies with levodopa and carbidopa

The sponsor noted that the original targeted indication for clinical use of perampanel was Parkinson's disease and therefore, combination studies with levodopa and carbidopa, which are commonly used to treat this disease, were conducted in rats and Cynomolgus monkeys.

A 13 week repeat dose combination study (perampanel/levodopa/carbidopa) in rats showed exaggerated pharmacology-induced CNS effects in all combination groups associated with trauma and the deteriorated health condition resulting in deaths. Slightly enhanced CNS clinical signs by the concomitant administration were related to increased exposure of perampanel in the combination group. Results indicated that concomitant administration did not induce any significant clinical pathology changes and organ toxicity in rats after 13 weeks. In Cynomolgus monkeys, 13 week combination repeat dose (perampanel/levodopa/carbidopa) did not induce any significant clinical pathology changes and organ toxicity although pharmacology related CNS clinical signs were slightly enhanced by concomitant treatment with perampanel.

Relative exposure

The clinical pharmacokinetic data for comparison with animal exposures in the toxicity studies were sourced from Study E2007-E044-009 (multiple dose study in healthy subjects). As clinical dosing will be daily, the most relevant clinical area under the concentration versus time curve (AUC) value was considered to be AUC from 0 to 24 h ($AUC_{0\text{-}24h}$) at steady state after repeated dosing, rather than AUC from 0 to 12 h ($AUC_{0\text{-}12h}$), AUC from 0 to infinity ($AUC_{0\text{-}inf}$) or single dose AUC values. Since Study E2007-E044-009 did not include the Maximum Recommended Human Dose (MRHD) of 12 mg/day, Day 21 exposure data from lower doses (6, 8, 10 mg/day) were normalised to 12 mg (Table 3).

Table 3. Derivation of clinical exposure parameters for comparison with animal values

Dose	Mean C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)
6 mg (n=8) [12 mg]	300.7 [601]	5567 [11134]
8 mg (n=8) [12 mg]	492.1 [738]	9037 [13556]
10 mg (n=8) [12 mg]	684.1 [821]	13517 [16220]
Means [12 mg]	720	13637

Table 4. Relative exposure to perampanel in toxicity studies by oral administration

Species	Study Dosing duration	Dose mg/kg/day	Sampling time	$AUC_{(0-24h)}$ (ng·h/mL)		C_{max} (ng/mL)		ER_{AUC}[a]		ER_{Cmax}[a]	
				Male	Female	Male	Female	M	F	M	F
Mouse/ICR Crj:CD-1(ICR)	C-B063 (2 weeks)	100	12 days	11466.0	11364.4	1750.1	1953.9	0.8	0.8	2.4	2.7
		300		20970.3	19988.3	2425.4	2131.8	1.5	1.5	3.4	3.0
		1000		33037.3	36521.8	3354.2	2314.7	2.4	2.7	4.7	3.2
	B-5121 (4 weeks)	3	25 days	1258.8	1478.8	454.1	639.6	0.1	0.1	0.6	0.9
		10		3507.4	3887.4	1190.9	1079.0	0.3	0.3	1.7	1.5
		30		7721.4	9676.6	1394.7	2286.9	0.6	0.7	1.9	3.2
		60		11146.4	9286.8	2213.1	2233.0	0.8	0.7	3.1	3.1
	B-4954 (13 weeks)	100	89 days	12976.1	10011.7	1976.5	2193.9	1.0	0.7	2.7	3.0
		300		18665.5	16163.5	2308.2	2747.6	1.4	1.2	3.2	3.8
		1000		14893.2	30534.1	2573.6	2899.6	1.1	2.2	3.6	4.0

Species	Study Dosing duration	Dose mg/kg/day	Sampling time	$AUC_{(0-24h)}$ (ng·h/mL)		C_{max} (ng/mL)		ER_{AUC}[a]		ER_{Cmax}[a]	
				Male	Female	Male	Female	M	F	M	F
Rat/SD IGS	TKB00006 (4 days)	10	4 days	603.0	3087.0	168	351.0	0.0	0.2	0.2	0.5
		100		8790.0	27567.0	965	1987.0	0.6	2.0	1.3	2.8
		300		15023.0	40950.0	1735	3950.0	1.1	3.0	2.4	5.5
	S00009 (4 weeks)	1	27 days	-	759.4	-	196.0	-	0.1	-	0.3
		3		-	-	-	-	-	-	-	-
		10		857.4	11267.3	208.4	1278.8	0.1	0.8	0.3	1.8
		30		2979.5	10287.1	535.8	1201.4	0.2	0.8	0.7	1.7
		100		11855.1	-	948.8	-	0.9	-	1.3	-
	S01008 (13 weeks)	1	85 days	631.8	998.5	167.3	255.6	0.0	0.1	0.2	0.4
		10		3243.2	4318.9	461.0	902.7	0.2	0.3	0.6	1.3
		30		5638.3	8454.1	502.0	1137.9	0.4	0.6	0.7	1.6
	S04007 (13 weeks)	60	28 days	7019.4	-	690.0	-	0.5	-	1.0	-
		100		6643.0	-	682.0	-	0.5	-	0.9	-
		300		31527.5	-	1807.4	-	2.3	-	2.5	-
Dog Beagle	TKB00008 (7 days)	1	7 days	550.0	337.0	112.0	75.0	0.0	0.0	0.2	0.1
		3		188.0	261.0	65.0	85.0	0.0	0.0	0.1	0.1
		10		534.0	512.0	133.0	131.0	0.0	0.0	0.2	0.2

Species	Study Dosing duration	Dose mg/kg/day	Sampling time	$AUC_{(0-24h)}$ (ng·h/mL)		C_{max} (ng/mL)		ER_{AUC}[a]		ER_{Cmax}[a]	
				Male	Female	Male	Female	M	F	M	F
	S00010 (4 weeks)	0.3	28 days	158.1	98.0	57.8	42.8	0.0	0.0	0.1	0.1
		1		221.8	343.4	75.7	106.0	0.0	0.0	0.1	0.1
		10		1222.5	3266.4	303.8	485.0	0.1	0.2	0.4	0.7
	S01009 (13 weeks)	0.1	91 days	21.6	49.3	9.0	13.5	0.0	0.0	0.0	0.0
		1		281.4	264.4	49.1	60.0	0.0	0.0	0.1	0.1
		10		905.5	913.1	148.8	122.9	0.1	0.1	0.2	0.2
Monkey Cynomolgus	TKB01016 (2 weeks)	0.5	14 days	1581.0	1848.5	154.9	193.3	0.1	0.1	0.2	0.3
		1		4197.9	2821.5	389.7	332.9	0.3	0.2	0.5	0.5
	SBL47-47 (4 weeks)	0.1	28 days	520.1	286.0	41.2	39.4	0.0	0.0	0.1	0.1
		0.3		1177.3	1116.4	108.8	118.8	0.1	0.1	0.2	0.2
		1		4526.4	3901.3	433.0	425.3	0.3	0.3	0.6	0.6
	SBL038-24 (39 weeks)	1	378 days	6286.8	5821.5	415.6	435.4	0.5	0.4	0.6	0.6
		1→2→4→8		13666.8	8108.4	870.8	663.7	1.0	0.6	1.2	0.9
		1→2→4→8		12089.7	12431.1	791.9	1098.3	0.9	0.9	1.1	1.5
	SBL-47-61 (52 weeks)	0.1	364 days	446.9	429.0	43.4	41.1	0.0	0.0	0.1	0.1
		0.3		2431.5	1493.4	171.2	123.1	0.2	0.1	0.2	0.2
		0.6		2777.5	3072.9	235.0	244.2	0.2	0.2	0.3	0.3

1. Steady state $AUC_{0\text{-}24h}$ and C_{max} values from clinical evaluation report ER2007-E044-009, where mean $AUC_{(0\text{-}24h)}$ and C_{max} values from the 6, 8 and 10 mg groups were normalised to a 12 mg dose, and the mean calculated used for relative exposure calculations; ER, animal/human exposure ratio based on AUC or C_{max}.

The animal/human relative exposures achieved in the toxicity studies were very modest, exceeding anticipated clinical exposure only in mice and rats (at high doses) but not in dogs and monkeys (Table 4). In the majority of studies, dose escalation was limited by clinical toxicity in all tested species and it is likely that increased exposure to test material may have been achieved only by more frequent dosing (>once daily), especially given the relatively short half-life of the compound in these species (1.4 to 6.9 h) compared to humans (105 h). Such alternative treatment regimens do not appear to have been explored. The relatively low clearance in humans compared to the test species may be attributable to higher plasma protein binding and lower intrinsic clearance but in any event this animal/human difference does limit the usefulness of the animal models. It is noted that differential plasma protein binding would increase the safety margins for the rat, dog and monkey (but not mouse) studies to some extent, since the free (active) fraction in human plasma is ≤ half the free fractions in the plasma of these test species.

Genotoxicity

Submitted studies showed that perampanel was negative in in vitro Ames assays and the in vitro mouse lymphoma assay, with or without metabolic activation. In view of the broad overlap in metabolic profile between rats and humans, the use of rat liver-derived S9 was appropriate in the in vitro studies. No clastogenic effects were induced by perampanel in an in vivo bone marrow micronucleus study in SD rats at ≥ 2000 mg/kg PO. Based on the standard acceptance criteria, the studies were considered valid and do not indicate any genotoxicity potential for perampanel.

Carcinogenicity

The mouse study found that perampanel increased mortality when administered orally for at least 85 weeks in males and up to 101 weeks in females. Results showed that there was an increased incidence of non-neoplastic inflammatory lesions associated with excessive grooming or self-trauma in skin/limbs/digits and penis (≥3 mg/kg) attributed to exaggerated pharmacologic effects of perampanel. Lower body weights were observed in males (30 mg/kg) and females (10 to 30 mg/kg). The rat study found low survival rates in males (100 mg/kg) with approximately 10% decrease in body weight in males (30 mg/kg) and females (10 mg/kg). All perampanel treatment groups had severe CNS clinical signs consisting of prostration, lateral position, decreased activity and abnormal gait considered to be related to the pharmacologic effects of perampanel. No significant differences in the incidences of neoplastic and non-neoplastic findings were found between the control and any dose group in either gender. Overall, the studies showed that perampanel was negative in both the mouse and rat 104 week carcinogenicity studies.

Plasma AUC was not determined in the rodent carcinogenicity studies. The high dose plasma concentrations which were measured at 13 and 26 weeks in these studies are about twice the estimated clinical C_{max} value of 720 ng/mL. A better estimate of relative exposure can be obtained by using the AUC data from the longest duration rodent studies that measured AUC at the high doses in the carcinogenicity studies to compare with the clinical AUC value.

Mice: HD (M) 30 mg/kg/day AUC 7721 ng.h/mL (Study B-5121; 4week study);
HD (F) 30 mg/kg/day AUC 9677 ng.h/mL (Study B-5121; 4 week study).

Rats: HD (M) 100 mg/kg/day, AUC 5710 ng.h/mL (Study SO4007; 13-week study);
HD (F) 30 mg/kg/day, AUC 8454 ng.h/mL (Study S01008; 13-week study).

HD=high dose (M)=male and (F)=female

All these AUC values are well below the clinical value at the MRHD (13637 ng.h/mL) and, apart from female mice, are also less than the clinical $AUC_{0\text{-}24h}$ at the 8 mg/day dose (9037 ng.h/mL; Table 3). It is possible that greater rodent exposure may have been achieved by using a different study design (for example, dosing more than once per day), although dose-limiting toxicity (observed even with once daily dosing) may have prevented further dose/exposure escalation. This low (relative to clinical) exposure achieved in the carcinogenicity studies was also highlighted in the sponsor's Nonclinical Overview. Appropriate statements have been recommended for incorporation into the Product Information document.

Reproductive toxicity

The fertility study in rats showed a decrease in body weight gain, and clinical signs such as abnormal gait were observed in males and females (10 mg/kg). Females showed prolonged and irregular oestrous cycles and consecutive diestrus (30 mg/kg), with no observed treatment related effects on fertility and early embryonic development. Male fertility was unaffected by treatment. The high dose in the fertility study (30 mg/kg/day) was approximately 23 times the MRHD, based on body surface area (see below).

In the rat and rabbit embryofetal development studies, pronounced decreases in body weight gain and food consumption were observed in both species (3 to 10 mg/kg), with actual body weight loss at the high dose in rabbits, along with treatment related CNS clinical signs (rats ≥ 1 mg/kg, rabbits 10 mg/kg). The numbers of implantation sites and live fetuses were decreased in rabbits (10 mg/kg), possibly secondary to the clear maternotoxicity at this dose. No evidence of teratogenicity was found in either rats or rabbits, apart from an increase in the incidence of diverticulum of the intestine in the rat study which, although not statistically significant, was dose related and a NOEL was not established. No historical control data from the testing laboratory were provided to assist interpretation of the significance of this finding, although databases for this species/strain suggest it is uncommon. Diverticulum of the intestine was also observed in the rat embryofetal development study in which levodopa/carbidopa were co-administered with the same doses of perampanel, although the finding was not dose related and was also found in a control group not treated with perampanel (see below).

The pre and postnatal development toxicity study in rats found clinical signs attributable to pharmacologic effects (≥ 1 mg/kg) in dams, with decreased body weight and food consumption, abnormal delivery, and abnormal nursing conditions (3 to 10 mg/kg). The number of stillbirths was increased, the birth index and the viability index (postnatal day 4 (PND4)) were reduced (3 to 10 mg/kg), and sexual maturation was delayed in male and female pups (10 mg/kg). There were no observed adverse effects on behavioural or reproductive functions in offspring due to treatment. It is possible that some of the adverse effects were secondary to maternotoxicity.

Relative exposure

There were limited toxicokinetic data supporting the reproductive toxicity studies (plasma exposure data in pregnant rabbits only). In the absence of other kinetic data for these studies, relative animal/human exposure was estimated by comparing oral doses based on body surface area (mg/m^2).

The rat fertility study used doses of 1, 10 and 30 mg/kg/day PO (6, 60 and 180 mg/m^2/day, respectively). The MRHD of 12 mg/day is equivalent to 0.24 mg/kg/day in a 50 kg adult, or approximately 7.9 mg/m^2/day. Thus, the rat doses represent 0.8, 8 and 23 times the MRHD, based on body surface area. The rat embryofetal development and pre/postnatal development studies used doses of 1, 3 and 10 mg/kg/day (6, 18 and 60 mg/m^2/day, respectively); these represent 0.8, 2 and 8 times the MRHD, based on body surface area. The rabbit embryofetal development study used doses of 1, 3 and 10 mg/kg/day (11, 33 and 110 mg/m^2/day, respectively) and these represent 1.4, 4 and 14 times the MRHD, based on body surface area. However, the kinetic data in pregnant rabbits indicate that the maximal exposure achieved at these doses was only 416 ng.h/mL (AUC) and 52 ng/mL (C_{max}), which are well below anticipated clinical exposure. This information has been recommended for inclusion in the Product Information document.

Combination toxicity with levodopa and carbidopa

The sponsor submitted combination embryofetal development studies with perampanel and levodopa/carbidopa in rats and rabbits.

The studies showed drug related CNS clinical signs in the combination groups (perampanel/levodopa/carbidopa or levodopa/carbidopa) and combination administration was associated with decreased body weight gain and decreased food consumption. In rats, there was no effect of treatment on the incidences of skeletal/visceral abnormalities; diverticulum of the intestine (observed in the perampanel-alone embryofetal development study, discussed above) was observed but without a clear relationship to treatment. Combination treatment in pregnant rabbits showed an increased incidence of visceral (retroesophageal subclavian artery) anomalies in all levodopa/carbidopa treated groups but no additional effects were observed when treatment was combined with perampanel. Overall, the studies indicated an enhancement of toxicity (CNS related clinical signs) by combination treatment of perampanel/levodopa/carbidopa in rats and monkeys and generally increased perampanel systemic exposure after repeated dosing (especially in rabbits) but no adverse effects on organ toxicity and no new findings for perampanel-associated embryofetal toxicity.

Pregnancy classification

The sponsor has proposed pregnancy Category B1[7]. The finding of diverticulum of the intestine in the rat embryofetal development study suggests that Category B3[8] would be more appropriate[9].

Juvenile toxicity and paediatric use

The results of the toxicity studies in juvenile rats and dogs indicate greater sensitivity to perampanel compared to adult animals. In immature (preweaning) rats, perampanel was found to induce CNS related clinical signs as in adult animals but also a reduction in growth progression (body weights, crown to rump lengths, femur/tibia lengths), decreased food consumption, and delayed sexual development, along with behavioural

[7] Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[8] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

[9] Although perampanel/levodopa/carbidopa co-treatment was not associated with this visceral abnormality in rats, its dose related occurrence in the perampanel-alone study at (likely) subclinical exposures without a NOEL warrants B3.

effects (reduced hind limb grip strength and foot splay, and an increased error rate in the Cincinnati water maze). Some of these effects persisted into the recovery phase. Reproductive parameters were not affected in the rats. Juvenile dogs were much less affected, exhibiting mainly pharmacology related clinical signs but no discernable effects on growth, behaviour or development. Exposure in juvenile rats was initially (postnatal day 7 (PND7)) considerably greater than that in adult rats but not at later times (≥PND35). In both species, however, the pharmacology related clinical signs were more pronounced/persistent in juveniles compared to adults at similar systemic exposures, indicative of greater sensitivity of the juveniles to perampanel.

Fycompa is not proposed for use in patients less than 12 years of age and it is uncertain to what extent these findings in immature animals can be interpreted in terms of potential risk for the proposed clinical use of perampanel in adolescents (12 to 18 years). The rats were very immature at commencement of dosing preweaning (the dogs less so) and extrapolation of adverse findings from such studies to the clinical treatment of a relatively much more developed human may not be meaningful, at least in the ≥12 year age group. Animal/human exposure comparisons are also problematic in view of the lack of clinical exposure data for adolescents. The juvenile animal studies should be re-visited for any future proposal to expand the patient group to include children <12 years. Nevertheless, given the adverse effects, it is recommended that relevant statements are included in the Product Information document, consistent with the FDA approved document.

Other toxicity studies

Dependence studies

The sponsor submitted toxicology studies investigating perampanel dependency in rats and rhesus monkeys. Rats administered perampanel daily over a period of 4 weeks showed signs of drug withdrawal, suggesting that perampanel had a physical dependence-producing potential. Observations of rhesus monkeys after IV self-administration regimen of perampanel showed relatively weak reinforcing effects. Results from a drug discrimination investigation in rats showed that perampanel did not engender interoceptive stimulus properties. The abuse potential of perampanel was shown to be lower than the controls used (ketamine and diazepam). Overall, the nonclinical studies suggest that perampanel may have the potential to cause physical dependence and weak reinforcing effects. Clinical studies investigating the abuse potential of perampanel will be assessed by the clinical evaluator.

Photo safety studies

The photo-safety of perampanel was investigated in bacteria (*Salmonella typhimurium*) (1 study), cells in vitro (2 studies; V79 and BALB/3T3), mice in vivo (a 13 week PO study) and guinea pigs in vivo (a 22 day topical study). In vitro studies showed positive results for perampanel in the neutral red uptake phototoxicity test and the chromosomal aberration test in Chinese Hamster V79 cells with ultraviolet (UV) irradiation. The result of the photo Ames assay was negative and there was no evidence of photo-irritation and photo-allergy studies in albino hairless guinea pigs. No evidence was obtained for photo-carcinogenic responses in a 13 week oral study in albino hairless mice or for photo-carcinogenic biomarkers in skin tissues from a 39 week chronic study in monkeys. Overall, the results from the photo-safety studies suggest that the risk for phototoxicity by perampanel appears to be very low or negligible in humans.

Impurities

All of the specifications for impurity levels comply with the relevant The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

Nonclinical summary

- The dossier included adequate nonclinical studies on the pharmacodynamics, pharmacokinetics and toxicity of perampanel according to relevant guidelines, with all definitive toxicity studies conducted under GLP conditions.
- Activation of AMPA receptors by glutamate, the primary central excitatory neurotransmitter implicated in neurological disorders caused by neuronal over-excitation, is thought to be responsible for most fast excitatory synaptic transmission in the brain. Primary pharmacology in vitro studies in cultured rat cortical neurons showed perampanel potently inhibits the AMPA-induced increase in intracellular free calcium concentration with minimal effect on NMDA-induced increases. Perampanel metabolites had weaker antagonistic effects.
- Primary pharmacology in vivo studies of various disease state models in mice, rats and primates were submitted. Perampanel was active in various seizure models (intracerebroventricular AMPA-induced, audiogenic, maximal electroshock, pentylenetetrazole (PTZ) induced) in mice and in kindling models in mice and rats, with no effect in the GAERS model in rats. Perampanel showed dose-dependent anti-allodynic effects in rat models, beneficial effects in EAE rodent models of multiple sclerosis and generally enhanced the effect of L-DOPA in rat and primate models of Parkinson's disease.
- Secondary pharmacodynamic studies showed that perampanel had no significant binding against a panel of 63 receptors, enzymes and other targets in vitro, suggesting it may be highly selective for the AMPA-type glutamate receptor with little/no affinity for other physiological targets. Perampanel had no significant binding in vitro to any of 86 receptor channel and transporter targets, with weak binding observed at the MT1(h) receptor (1 mg/mL), as well as A1(h), A2A(h), A3(h), BZDc, GABAA, MT1(h), ML2(MT3), M1(h), k(KOP) and 5-HT1A(h) receptors (10 mg/mL). Perampanel dose-dependently increased motor uncoordination mice and rats (respective ED_{50} 1.8 and 9.1 mg/kg). There is reasonable supporting nonclinical evidence that perampanel is a potent, selective, non-competitive AMPA-type glutamate receptor antagonist.
- Safety pharmacology studies reported CNS depressant effects in rats, confirmed in the toxicity studies. No adverse cardiovascular effects were detected in dogs (10 mg/kg PO), although plasma exposure would have been low relative to clinical levels. An in vitro hERG assay reported a generous safety margin for inhibitory concentrations relative to clinical exposure (especially the unbound plasma concentration), indicative of low potential for QT prolongation.
- Pharmacokinetics in rats, dogs and monkeys indicate that perampanel has a low to moderate clearance and a moderate to large volume of distribution with no accumulation observed after repeated dosing. Perampanel-associated radioactivity showed very long residence times for aorta (rat) and eyeball (rat, monkey) (respective half-lives 110 and 45 weeks in rats) but no histopathologic findings or adverse toxicology were reported for these tissues. Distribution studies in pregnant and lactating rats noted placental transfer and excretion into milk of perampanel and/or its metabolites.
- The major plasma component was unchanged drug in rats, monkeys and humans, and a similar metabolic profile was demonstrated in the test species and humans. Primary oxidative metabolism was mediated by CYP3A4/5, with up to 16 metabolites reported across studies. In vitro, perampanel weakly induced CYP3A4/5 (and CYP2B6), and weakly inhibited CYP2C8 and UGT1A9 and transporters OAT1, OAT3, OCT1, P-gp and BCRP, suggestive of low interactive potential with other medicines. Excretion was mainly faecal in rats and monkeys.

- In single dose PO toxicity studies, no deaths occurred at mg/kg doses up to 1500 (mice), 1000 (rats; 2000 lethal in females), 300 (rabbits), 10 (dogs) and 4 (monkeys). In rodents, clinical signs included pharmacology-based CNS effects consisting of abnormal gait, decreased activity, prostration, dyspnea (mice only), bradypnea and hypothermia (rats only), as well as mydriasis (rats only). Dogs administered the MTD of 3 mg/kg and monkeys administered the MTD of 2 mg/kg showed severe pharmacology based CNS clinical signs such as ataxia and prostration.
- Repeat dose studies (mice, rats, dogs, monkeys) showed similar CNS based clinical signs, attributed to the pharmacology of the drug (such as abnormal gait, hypoactivity, prostration and somnolence). There were deaths in mice (≥ 60 mg/kg) and rats (males 100 to 300 mg/kg; females 30 mg/kg) but not dogs or monkeys at the tested doses. No adverse clinical pathology or histopathology was reported in the test species although dose levels were limited by clinical toxicity and resultant systemic exposures were low relative to anticipated clinical values (plasma AUC exceeded clinical AUC only at high doses in rodents). Combination treatment with perampanel, levodopa and carbidopa in rats and monkeys showed enhanced clinical signs.
- Perampanel was negative in bacterial reverse mutation (Ames) and mouse lymphoma assays in vitro with or without metabolic activation, and the in vivo bone marrow micronucleus assay in SD rats. There was no evidence of tumourigenicity in 104 week PO studies in mice and rats, although estimated systemic exposures achieved were less than clinical exposure.
- There were no effects on male or female fertility or early embryonic development in rats, although females had prolonged/irregular oestrous cycles and consecutive diestrus. Embryofetal development studies in rats and rabbits were associated with maternal toxicity, which likely contributed to some embryofetal toxicity at high doses. There was no evidence of teratogenic potential in rats or rabbits, with the possible exception of a dose related increased incidence of divertculum of the intestine at all tested doses in a perampanel alone rat study[10], which was not confirmed in a perampanel/levodopa/carbidopa combination study. A pre/postnatal development study in rats noted abnormal delivery and nursing, increased stillbirths, and reduced birth/viability indices, concomitant with clinical toxicity of dams but there were no treatment related adverse effects on behaviour or reproductive functions in offspring. Toxicokinetic data were not available for the reproductive studies but systemic exposure was likely to have been subclinical.
- Juvenile rats and dogs showed greater sensitivity to perampanel than adults with regard to pharmacology related clinical signs. In pre weaning rats, perampanel reduced growth progression (body weight, crown-to-rump length, femur/tibia length) and delayed sexual development, along with some behavioural effects but reproductive parameters were not affected. These effects were not seen in juvenile dogs.
- Limited studies in rats and monkeys suggested a potential for physical dependence and weak reinforcing effects.
- The results of various phototoxicity tests were mostly negative, suggestive of low phototoxic potential.
- There are no nonclinical concerns regarding the specification limits of impurities.

[10] This finding was also included in the Pregnancy section of the FDA Approved Labelling (11 June 2013).

Conclusions and recommendation

- The nonclinical dossier included the relevant numbers and types of studies to support registration of a new chemical entity and the pharmacology studies were supportive of the proposed indication. The main issues arising from the nonclinical data are highlighted below.
- Systemic exposures achieved in the animal studies of long-term toxicity, carcinogenicity and reproductive toxicity were generally less than anticipated clinical exposure due to dose limiting clinical toxicity and target organs of toxicity have not been identified. Rodent carcinogenicity studies were negative, although exposures achieved were less than clinical exposure. Adequate genotoxicity testing was negative.
- The adequate safety margin in a hERG *in vitro* assay suggested only a low QT prolongation liability but in vivo nonclinical confirmation was limited (low exposure) and clinical confirmation will be required.
- The clinical significance of the prolonged residence time of drug related material in aorta and eyeball is unknown. Medicines which accumulate in aorta can have cardiovascular toxicity (for example, rofecoxib). Additional studies to investigate the ability of perampanel to bind to the human aorta have been recommended.
- In view of the visceral abnormality (diverticulum of the intestine) in 1 of 2 rat embryofetal development studies, a pregnancy Category of B3 is considered prudent at this stage (B1 was proposed by the sponsor).
- A possible dependence liability has been noted in animal studies.
- Limitations of the nonclinical data may be allayed by adequate clinical data.
- The nonclinical evaluator also recommended amendments to the draft Product Information document but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Partial epilepsies (focal or localization-related) account for more than 60% of epilepsies, and they include most of the difficult-to-treat subjects. Partial epilepsies include simple partial seizures (without impairment of consciousness), complex partial seizures (with impairment of consciousness and often more disabling), and secondarily generalized tonic-clonic seizures.

The goals of treatment for adults with epilepsy are the best quality of life achievable, with no seizures, and the fewest possible adverse effects from treatment.

> *'Approximately 30% of patients continue to experience inadequate seizure control with current treatments. Data from studies investigating the efficacy of new AEDs as adjunctive therapy in patients refractory to standard therapies showed that the highest doses of the most efficacious of these adjunctive AEDs (topiramate, oxcarbazepine, levetiracetam, and pregabalin) resulted in a 50% or greater reduction in seizure frequency in only about one-third of patients, after accounting for the placebo response. Furthermore, seizure control in many patients comes at the*

price of troublesome or serious side effects. Up to 25% of patients initially exposed to an AED have an adverse event (AE) severe enough to require drug withdrawal, and many more experience chronic AEs that negatively impact their quality of life. Thus, there clearly remains a significant unmet need for new AEDs with improved efficacy and tolerability profiles, as well as for greater mechanistic diversity.[11]

AMPA receptors play a key role in mediating cortical glutamatergic transmission. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially anti-epileptogenic effects. Perampanel has shown anticonvulsant activity in seizure models in rodents, suggesting that perampanel could be effective in the treatment of partial-onset seizures, with or without secondary generalization.'

Comment: In the section on Analysis of Anti-Epileptic Drugs' Mechanism of Action[12] it is suggested that the median Responder Rates and Reduction in Seizure Frequency are greater with perampanel than placebo regardless of concomitant anti-epileptic drug (AED) action on the sodium channel; however the number of subjects on concomitant non-sodium channel mechanism of action AEDs are small.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- 27 Phase I and two Phase II clinical pharmacology studies, and 4 that provided pharmacodynamic data.
- In addition PK data obtained in Phase II studies 206 and 208 and the pivotal Phase III studies 304, 305, and 306 were utilized in the population PK, PD, or PK/PD analyses.
- 3 pivotal efficacy studies (304, 305, and 306) [studies 206 and 208 also contained efficacy secondary variables].
- 3 ongoing, open-label extension studies 207 [of Studies 206 and 208], 307 [of Studies 304, 305, and 306], 233 [of Study 231]).
- Dose-finding Study 206.
- Incomplete Study 235 for deaths and serious adverse events only.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies in the perampanel clinical development program were conducted in compliance with Good Clinical Practice guidelines.

[11] Sponsor's Clinical Overview
[12] Sponsor's Summary of Clinical Efficacy

Pharmacokinetics

Studies providing pharmacokinetic data

No PK study had deficiencies that excluded their results from consideration. Table 5 shows the studies relating to each PK topic.

Table 5. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK- Single dose	E2007-E044-001 E2007-J081-010	 *
	General PK - Multi-dose	E2007-E044-002 E2007-E044-009 E2007-J081-026	* * *
	Bioequivalence - Single dose	E2007-A001-008 E2007-E044-016 E2007-E044-037 E2007-A001-039 E2007-A001-040	* * * * *
	Bioequivalence - Multi-dose	n/a	
	Bioavailability - Single dose	E2007-E044-017 E2007-E044-028	* *
	Food effect – Single dose	E2007-E044-003 E2007-E044-009	* *
PK in special populations	Target population - Single dose	n/a	
	- Multi-dose	E2007-E049-203 E2007-J081-231	§
	Hepatic impairment	E2007-E044-015	*
	Renal impairment	n/a	
	Paediatrics and adolescents	n/a	
	Elderly – Single dose	E2007-E044-007 E2007-E044-004	*
	Poly-substance users	E2007-A001-023 E2007-A001-024	* *

PK topic	Subtopic	Study ID	*
Gender-related PK	Males versus females	E2007-E044-003	*
PK interactions	Ketoconazole	E2007-E044-005	*
	Carbamazepine	E2007-E044-006	*
	Midazolam	E2007-A001-014	*
	Oral contraceptives	E2007-E044-019 E2007-E044-029	* *
	Levodopa	E2007-E044-025	*
Population PK analyses	Healthy subjects	CPMS-E2007-2011-002[a]	*
	Target population · Adults (Phase II) · Adults (Phase III) · Adolescents (Phase III)	EMFFR2008/06/00[b] CPMS-E2007-2011-003[c] CPMS-E2007-2011-004[d]	§ § §

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. [a] Studies included in this analysis were 001, 002, 003, 004, 005, 006, 008, 009, 010, 013, 015, 016, 023, 024, 026, 028, 029, 030 and 037. [b] Two Phase II studies (206 and 208) were included in the analysis.

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of perampanel are not well characterised in terms of distribution, bioavailability and elimination. Apparent volume of distribution could not be accurately determined in the Population Pharmacokinetics (Pop-PK) analysis and the multi-phasic and long elimination phase(s) make elimination half-life (and elimination rate constant) very difficult to determine for perampanel. An absolute bioavailability of 116% is nonsensical and is explained, in part, by deviation from the standard methods utilised in the determination of absolute bioavailability as well as the use of different assays to measure the relative AUC indices. In terms of bioavailability among clinical trial and proposed marketing formulations, it was evident that the higher strength, the larger tablets (6 mg and 12 mg), did not achieve an equivalent C_{max} to the 2 mg perampanel tablet. This is reflected in the sponsor's sample size calculations in Studies 039 and 040 that used a 'true ratio estimate' of 0.9 instead of 1.0, which is what is expected for true bioequivalence.

The determination of elimination half-life was not clear from this submission. The wash-out period of 2 weeks in many drug-drug interaction studies undertaken with perampanel assumed the half-life occurred in the range 70 to 100 hours (that is, steady-state at 14 days). However, this 2 week period was insufficient in most instances. The drug-drug interaction studies deviated from standard practice by not employing a true cross-over design but instead used a fixed sequence design on the basis of the long elimination half-life making study duration impractical. Using a fixed sequence design has the potential to introduce period effects as well as carryover effects that may impact on the validity of the results. Several studies reported quantifiable plasma perampanel at pre-dose (some with

C_{max} > 5%) which suggests the wash-out period was insufficient as well as a longer elimination half-life than predicted. Some studies had quantifiable plasma perampanel concentrations after a 6 week washout, which again suggests a longer half-life than the sponsor proposes in its PI (105 h). The long elimination half-life may be potentially problematic in dose changes for some individuals (especially those with any degree of liver impairment) and in the treatment of overdose.

Dose-proportionality was generally satisfactory over the proposed range (2 to 12 mg/day, inclusive). Metabolic clearance was the primary mechanism of elimination of parent perampanel. The faecal route was the primary route of elimination (then renal). No active metabolites of perampanel were identified.

The sponsor proposes to register perampanel for use in adolescents and adults (including elderly patients) for partial seizures, yet the PK data for adolescents at least is limited to sparse PK data in subjects with partial seizures. There are no specific PK studies in healthy adolescents and the sponsor does not appear to have analysed the 74 adolescent subjects by age group (12 to 14, 15 to17 years), so it is unclear whether younger adolescent subjects have different PK profiles compared with their older peers. The results in the elderly populations studied (albeit small in numbers) are inconclusive. Study 007 suggested exposure and half-life of perampanel could be two fold greater than an adult population but these results were not supported by Study 004. On this basis dosing in the elderly should proceed more cautiously than in the general adult population.

Food affects the rate of absorption but not the extent of exposure so dose adjustment is not required. While females tended to have 24% lower apparent clearance than males, this is unlikely to be clinically significant. Race and body size did not appear to markedly affect clearance, although there is a suggestion from the evidence provided that clearance may be reduced in adipose tissue, which may have implications for dose adjustment in subjects with high body mass index (BMI). Timing of dosing did not greatly affect PK parameters but given the association of C_{max} with sedation, evening dosing is appropriate.

Drug-drug interaction studies revealed a very significant interaction with cytochrome P450 isozyme CYP3A4 inducers, particularly carbamazepine (more rapid clearance, reduced exposure) as well as the progesterone component of the combined oral contraceptive and possibly clinically significant interactions with ketoconazole and midazolam at higher doses of perampanel. No drug-drug interaction was observed with levodopa.

Pharmacodynamics

Studies providing pharmacodynamic data

No clinical studies were submitted that explored the primary pharmacology of perampanel. The following table lists the other pharmacodynamic studies submitted.

Table 6. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Secondary Pharmacology	Effect on Sedation	001, 002, 003, 004, 009, 010, 026, 030, 203 CPMS-E2007-2011-003	*
Gender other genetic and Age-	Effect of gender	n/a – see subgroup analyses of efficacy studies	

PD Topic	Subtopic	Study ID	*
Related Differences in PD Response	Effect of age	n/a – see subgroup analyses of efficacy studies	
PD Interactions	Alcohol	030	*
	Sedation, psychomotor, postural stability, EEG, cognitive function	001, 002, 009, 030	
	Phototoxicity	020	*
	Carbamazepine	006	§
	Abuse liability	023, 024	*
	Thorough QT study	013	*
Population PD and PK-PD analyses	Healthy subjects	CPMS-E2007-2011-002	
	Target population · Adults · Adolescents	CPMS-E2007-2011-003 EMFFR2008/06/00 SCPMS-E2007-2011-004	§

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacodynamics

No primary pharmacodynamic studies were undertaken. The anticonvulsant effects of perampanel are inferred from the seizure frequency observed in efficacy studies.

Dose related sedation and effects on psychomotor performance were demonstrated in this submission, with maximal effects generally evident at C_{max}. This lends support to an evening once daily dosing of perampanel. Higher doses of perampanel appeared to affect body sway/postural stability, which may become an issue in elderly patients prone to falls. However, the Pop-PK analysis in 74 adolescent subjects did not demonstrate any perampanel exposure-adverse event (AE) relationships. Lack of association with somnolence for example is probably due to the small numbers of adolescent subjects. Furthermore, no analysis by adolescent sub-group (for example 12 to 14 years, 15 to 17 years) was undertaken to determine if there were differences in younger versus older adolescents (in terms of PD as well as PK).

There were significant pharmacodynamic interactions with carbamazepine and alcohol (and presumably even greater effects with all three agents together). Patients co-prescribed carbamazepine and perampanel or consuming alcohol while taking perampanel (especially in combination with carbamazepine) should be made aware of the apparent 'synergistic effects' on sedation and cognitive function, as they may affect an individual's ability to drive or operate machinery.

From the data presented in this application, perampanel appears to have low arrhythmogenic potential (minimal effect on QT interval[13]), no apparent effect on inducing an immediate or delayed skin phototoxicity reaction and low potential for drug abuse (perampanel considered equivalent to a benzodiazepine). There is some evidence to suggest withdrawal effects in subjects who received high perampanel doses but its significance is unclear.

Dosage selection for the pivotal studies

From Study 304 Report

> *'The results of the PK/PD analysis of Studies 206 and 208 were used to select the doses to evaluate in the Phase III studies (no effect = 2 mg, minimum effective dose = 4 mg, mid-range effective dose = 8 mg and high effective dose = 12 mg).*
>
> *Study 206[14] demonstrated: 1) a trend in therapeutic effect (31% with perampanel versus 22% with placebo, P = 0.19, for the primary analysis of responder rate), 2) this effect size is within the range of other AEDs when studied in their lower dose range, 3) perampanel at a 4 mg dose was well tolerated with an AE rate similar to that with placebo. The rate of subject discontinuation was 6% in both treatment arms.*
>
> *Study 208[15] demonstrated greater treatment effects with acceptable tolerability at doses up to and including 12 mg/day. Results of the PK/PD analysis of these two studies were used to select the doses to evaluate in the Phase III studies. All three studies include titration periods when the doses are adjusted upward to the randomly assigned dose and dose adjustments were permitted subsequently based on the occurrence and resolution of intolerable AEs.'*

Efficacy

Studies providing efficacy data

Three pivotal double-blind, placebo-controlled, dose-escalation, parallel-group studies to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures were performed. These studies are described in the CER Attachment 2. These studies used similar designs but different doses of perampanel and were designed to be pooled:

- Study 306: subjects were given perampanel at doses of 2 mg, 4 mg, and 8 mg daily
- Studies 305 and 304: subjects were given 8 mg and 12 mg perampanel daily.

Evaluator's conclusions on efficacy

In the pivotal trials patients had to be on stable doses of 1, 2 or 3 anti-epileptic drugs (AEDs) for ≥ 21 days or for a new AED regime ≥ 49 days and despite this treatment[16] have had five or more partial seizures (with two or more partial seizures per each 3 week period) and no 25 day seizure free period in the 6 week period Pre-randomization Phase.

[13]The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death.
[14]A Phase II, double-blind, placebo-controlled, dose-escalation (to a maximum of 4 mg/d), parallel-group study of perampanel given as adjunctive therapy in subjects with refractory partial seizures
[15]A second, Phase II, escalating-dose trial
[16] 749 (50.7%) were on 2 AEDs, and 523 (35.4%) were on 3 AEDS

> The commission has determined that Class I superiority studies be designed to detect a >20% absolute (rather than relative) difference in the primary outcome (that is, efficacy/effectiveness) between study treatment and comparator using an intent-to-treat analysis.[17]

While this recommendation is in relation to monotherapy,[18] it is consistent with the basis of the sample size calculations in the pivotal studies.

> It was assumed that the percent change in seizure frequency per 28 days in the Maintenance Period relative to the Pre randomization Phase would be 10% in the placebo group and 32% in the 8 mg group in the Intent-to-Treat (ITT) Analysis Set. Therefore, a sample size of 120 subjects in each treatment group in the ITT Analysis Set would have 83% power to detect a treatment difference of 22% in seizure frequency.

Not all the median or mean results for ≥ 4 mg once daily (OD) treatment groups in the pivotal studies achieved the 20% separation in percent change in seizure frequency per 28 days, however there was consistent statistically significant difference shown by the p values.

With the responder rate, Study 304 failed to show any statistically significance from placebo for either 8 or 12 mg while Study 305 did with differences from placebo approaching 20%; Study 306 showed for 4 and 8 mg groups statistically significant differences from placebo approaching 20% for the 8 mg group.

The sponsor's explanation for the results in Study 304 related them to a higher placebo response in 2 South American centres.

The effect of sex and race do not appear to be significant.

There are insufficient elderly patients for comment.

> Efficacy needs to be evaluated for all focal seizures and secondary generalised seizures separately.[19]

Studies 304 and 305 showed statistically significant differences > 20 % from placebo in both percent change in seizure frequency per 28 days and responder rate for patients with secondarily generalised seizures while Study 306 could show no significant difference.

There were 124 adolescents enrolled in the trials with descriptive summary results only; a study in adolescents was ongoing at the time of submission. In the Phase III Double-blind Studies 58 adolescents were on ≥ 4 mg/day of perampanel.

The pivotal studies were of sufficient length for showing efficacy and long term sustainment of effect was seen in the extension studies with 588 subjects at 1 year.

[17] Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes *T Glauser et al, Epilepsia, 54(3):551–563, 2013

[18] Approximately 60% of newly diagnosed patients are seizure-free on a single AED (monotherapy). An additional 10%-20% achieve freedom of seizure with polytherapy. It follows that about 30% of patients are not satisfactorily controlled. In addition many patients suffer from significant adverse effects. CHMP/EWP/566/98 Rev. 2/Corr Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders Replaces: CPMP/EWP/566/98 Rev 1 (adopted by TGA 19 April 2001) page 3

[19] CHMP/EWP/566/98 Rev. 2/Corr Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders Replaces: CPMP/EWP/566/98 Rev 1 (adopted by TGA 19 April 2001) page 7

Safety

Studies providing safety data

Studies that assessed safety as a primary outcome

- Study E2007-G000-307 [Extension of Studies 304, 305, and 306],
- Study E2007-A001-207 [Extension of Studies 206 and 208],
- Study E2007-J081-233 [Extension of Study 231],
- Study E2007-G000-208, Study E2007-A001-206 Study E2007-J081-231.
- Study E2007-E049-203 a PK study in patients.

Other studies evaluable for safety only

Incomplete Study 235 for deaths and serious adverse events only.

Clinical pharmacology studies

27 Phase I clinical pharmacology studies.

Safety issues with the potential for major regulatory impact

Liver toxicity

Study 015 was a study of the effect of impaired hepatic function on the PKs of a single 1 mg dose of perampanel. One out of six subjects with moderate hepatic impairment had a mild adverse event (AE) (headache), considered possibly related, while three out of twelve normal subjects each had 1 AE (nausea, fatigue, and headache); all possibly related to study drug.

Markedly abnormal results occurred in ≤ 3.1% of the subjects in any treatment group. When the analysis was limited to subjects whose baseline values were within the normal range markedly abnormal results occurred in ≤ 1.1% of the subjects in any treatment group.

> Comment: Based on this statement, patients with abnormal liver function are approximately twice as likely to have deterioration in hepatic markers.

In the double-blind studies, none of the AEs related to hepatobiliary parameters were serious AEs (SAEs) and none caused discontinuation. Alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased each led to discontinuation of treatment in 1 placebo subject.

Markedly abnormal high cholesterol values occurred in one (0.2%) subject in the placebo group and 20 (2.0%) subjects in the total perampanel group. Fifteen of the latter 20 subjects did not have markedly abnormal values for cholesterol at two consecutive visits. Of the five subjects with markedly abnormal values at two or more consecutive visits, all had baseline values for cholesterol that were above the normal range, and none had a change from baseline of more than one NCI grade[20].

[20]The National cancer Institute (NCI) Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.

In the epilepsy all treated pool, none of the AEs related to hepatobiliary parameters occurred were SAEs and no subject discontinued treatment due to such AEs.

Table 7. Treatment-Emergent Markedly Abnormal Laboratory Results for Hepatobiliary Parameters by Randomized Treatment – Epilepsy Phase III Double-blind Pool (Safety Analysis Set)

		Perampanel[a]				
Laboratory Test (Unit)	Placebo[a] (N=442) n (%)	2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
ALANINE AMINOTRANSFERASE (IU/L)						
n[b]	430	179	168	422	246	1015
Markedly Abnormal High	1 (0.2)	0	1 (0.6)	1 (0.2)	0	2 (0.2)
ALKALINE PHOSPHATASE (IU/L)						
n[b]	431	179	169	422	246	1016
Markedly Abnormal High	0	0	0	0	0	0
ASPARTATE AMINOTRANSFERASE (IU/L)						
n[b]	430	179	168	421	246	1014
Markedly Abnormal High	0	1 (0.6)	2 (1.2)	2 (0.5)	0	5 (0.5)
BILIRUBIN (TOTAL) (UMOL/L)						
n[b]	431	179	169	422	246	1016
Markedly Abnormal High	0	2 (1.1)	0	0	0	2 (0.2)
GAMMA GLUTAMYL TRANSFERASE (IU/L)						
n[b]	431	179	169	422	246	1016
Markedly Abnormal High	12 (2.8)	4 (2.2)	3 (1.8)	13 (3.1)	7 (2.8)	27 (2.7)

An increase in NCI grade to Grade 2 or higher from baseline constitutes a markedly abnormal result. Subjects are counted only once for each row. [a]: Subjects treated during the double-blind study. [b]: Indicates the number of subjects with observed data during the treatment period and is used for calculating the percent.

Table 8. Treatment-Emergent Markedly Abnormal Laboratory Results for Hepatobiliary Parameters – Epilepsy All Treated Pool (Safety Analysis Set)

Laboratory Test (Unit)	Total Perampanel[a] (N=1639) n (%)
ALANINE AMINOTRANSFERASE (IU/L)	
N[b]	1577
Markedly Abnormal High	7 (0.4)
ALKALINE PHOSPHATASE (IU/L)	
N[b]	1577
Markedly Abnormal High	0
ASPARTATE AMINOTRANSFERASE (IU/L)	
N[b]	1576
Markedly Abnormal High	8 (0.5)
BILIRUBIN (TOTAL) (UMOL/L)	
N[b]	1576
Markedly Abnormal High	2 (0.1)
GAMMA GLUTAMYL TRANSFERASE (IU/L)	
N[b]	1565
Markedly Abnormal High	68 (4.3)

An increase in NCI grade to Grade 2 or higher from baseline constitutes a markedly abnormal result. Subjects are counted only once for each row. [a]: Subjects treated with perampanel in any study. [b]: Indicates the number of subjects with observed data during the treatment period and is used for calculating the percent.

Renal

In the Epilepsy Phase III Double-blind Pool the mean changes from baseline to the end of treatment were small; there were no notable differences between the treatment groups (including placebo) and no dose related trends. Markedly abnormal high values for creatinine occurred in 1 (0.2%) placebo subject and 2 (0.2%) perampanel subjects. When the analysis was limited to subjects whose baseline values were within the normal range, markedly abnormal values for creatinine occurred in 1 (0.2%) and 1 (0.1%) subjects, respectively.

In the double-blind studies, none of the AEs related to renal parameters were SAEs and none led to discontinuation of treatment.

In the Epilepsy All Treated Pool markedly abnormal high values for creatinine were seen in 9 (0.6%) subjects in the total perampanel group (2 of these had abnormal values at baseline).

Of the 13 abnormal creatinine assessments that occurred in the total perampanel group, 3 (0.2%) occurred with doses of < 4 mg/day, 3 (0.2%) occurred with doses of 4 mg/day, and 7 (0.2%) occurred with doses of > 8-12 mg/day.

In the epilepsy all treated pool, AEs related to renal parameters occurred in < 0.3% of the subjects, none were SAEs. There was a related AE (blood creatinine increased) that led to discontinuation of treatment in one subject.

Rash

In the epilepsy Phase III double-blind pool, there were no deaths or SAEs related to rash. Five (0.5%) perampanel subjects discontinued due to AEs related to rash. The doses at the onset of these events were 2 mg/day (1 rash erythematous), 6 mg/day (1 rash), 8 mg/day (2 subjects with rash), and 12 mg/day (1 rash). There were no SAEs related to rash.

In the epilepsy all treated pool, rash occurred in 1.8% of placebo subjects and 3.3% of total perampanel subjects in the combined double-blind studies. The exposure-corrected rates were 0.004 and 0.003 subjects with rash per subject-month, respectively. Ten (0.6%) subjects in the total perampanel group discontinued treatment due to AEs related to rash.

Table 9. Adverse Events (for Rash) by Decreasing Frequency and Randomized Treatment – Epilepsy Phase III Double-blind Pool (Safety Analysis Set)

		Perampanel[a]				
MedDRA Preferred Term[b]	Placebo[a] (N=442) n (%)	2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Subjects with any TEAE	9 (2.0)	2 (1.1)	7 (4.1)	14 (3.2)	6 (2.4)	29 (2.8)
Rash	7 (1.6)	2 (1.1)	4 (2.3)	12 (2.8)	5 (2.0)	23 (2.2)
Rash Papular	0	0	2 (1.2)	1 (0.2)	0	3 (0.3)
Rash Erythematous	1 (0.2)	0	0	0	1 (0.4)	1 (0.1)
Rash Pruritic	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Rash Generalized	0	0	1 (0.6)	0	0	1 (0.1)
Rash Maculo-Papular	0	0	1 (0.6)	0	0	1 (0.1)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period. Subject with two or more adverse events with the same preferred term is counted only once for that preferred term. [a]: Subjects treated during the double-blind study. [b]: MedDRA preferred terms are sorted in descending order of frequency in the total perampanel column.

Table 10. Adverse Events (Selected Preferred Terms for Rash) by Decreasing Frequency – Epilepsy All Treated Pool (Safety Analysis Set)

MedDRA Preferred Term[b]	Total Perampanel[a] (N=1639) n (%)
Subjects with any TEAE	61 (3.7)
Rash	54 (3.3)
Rash Papular	3 (0.2)
Rash Pruritic	2 (0.1)
Rash Erythematous	1 (0.1)
Rash Generalized	1 (0.1)
Rash Macular	1 (0.1)
Rash Maculo-Papular	1 (0.1)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period. Subject with two or more adverse events with the same preferred term is counted only once for that preferred term. [a:] Subjects treated with perampanel in any study. [b]: MedDRA preferred terms are sorted in descending order of frequency in the total column.

Cardiovascular safety

In the epilepsy Phase III double-blind pool there were no cardiac or ECG related deaths or SAEs. There were 3 discontinuations; 1 in the placebo group due to palpitations, 1 in the 2 mg/day group due to tachycardia and 1 in the 8 mg/day group due to ECG QT prolonged.

In the epilepsy all treated pool there was 1 cardiac related death. SAEs each in a single perampanel subject were; bradycardia and sick sinus syndrome, angina pectoris, atrial fibrillation and atrial flutter, acute coronary syndrome, angina unstable, atrioventricular dissociation and hypertrophic cardiomyopathy, coronary artery stenosis and heart rate irregular, myocardial infarction.

Discontinuations due to AE each in a single perampanel subject were: atrioventricular block first degree, bradycardia, sinus bradycardia, tachycardia, ECG QT prolonged, blood pressure increased.

Table 11. Adverse Events (Selected Preferred Terms for Cardiac and ECG AEs) by Decreasing Frequency and Randomized Treatment – Epilepsy Phase III Double-blind Pool (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Placebo[a] (N=442) n (%)	Perampanel[a] 2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Subjects with any TEAE	13 (2.9)	5 (2.8)	1 (0.6)	14 (3.2)	6 (2.4)	26 (2.5)
Cardiac Disorders	10 (2.3)	4 (2.2)	1 (0.6)	9 (2.1)	4 (1.6)	18 (1.7)
Bradycardia	3 (0.7)	1 (0.6)	1 (0.6)	1 (0.2)	1 (0.4)	4 (0.4)
Tachycardia	1 (0.2)	1 (0.6)	0	1 (0.2)	2 (0.8)	4 (0.4)
Sinus Bradycardia	3 (0.7)	1 (0.6)	0	1 (0.2)	0	2 (0.2)
Angina Pectoris	0	0	0	2 (0.5)	0	2 (0.2)
Palpitations	2 (0.5)	0	0	1 (0.2)	0	1 (0.1)
Arrhythmia	0	0	0	1 (0.2)	0	1 (0.1)
Atrial Fibrillation	0	0	0	1 (0.2)	0	1 (0.1)
Bundle Branch Block Left	0	0	0	0	1 (0.4)	1 (0.1)
Conduction Disorder	0	0	0	1 (0.2)	0	1 (0.1)
Dilatation Atrial	0	1 (0.6)	0	0	0	1 (0.1)
Atrioventricular Block First Degree	1 (0.2)	0	0	0	0	0
Sinus Tachycardia	1 (0.2)	0	0	0	0	0
Investigations	3 (0.7)	1 (0.6)	0	5 (1.2)	2 (0.8)	8 (0.8)
Electrocardiogram QT Prolonged	0	0	0	3 (0.7)	0	3 (0.3)
Blood Pressure Diastolic Decreased	2 (0.5)	0	0	1 (0.2)	0	1 (0.1)
Electrocardiogram QRS Complex Prolonged	1 (0.2)	0	0	1 (0.2)	0	1 (0.1)
Electrocardiogram Abnormal	0	1 (0.6)	0	0	0	1 (0.1)
Electrocardiogram ST Segment Elevation	0	0	0	1 (0.2)	0	1 (0.1)
Electrocardiogram ST-T Segment Abnormal	0	0	0	0	1 (0.4)	1 (0.1)
Electrocardiogram T Wave Abnormal	0	0	0	0	1 (0.4)	1 (0.1)
Heart Rate Decreased	0	0	0	0	1 (0.4)	1 (0.1)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period. Subject with two or more adverse events with the same preferred term is counted only once for that preferred term. [a]: Subjects treated during the double-blind study.

Table 12. Adverse Events (Cardiac and ECG AEs) by Decreasing Frequency – Epilepsy All Treated Pool (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Total Perampanel[a] N=1639 n (%)	MedDRA System Organ Class Preferred Term	Total Perampanel[a] N=1639 n (%)
Subjects with any AE	67 (4.1)	Hypertrophic Cardiomyopathy	1 (0.1)
Cardiac Disorders	50 (3.1)	Left Ventricular Hypertrophy	1 (0.1)
Bradycardia	10 (0.6)	Myocardial Infarction	1 (0.1)
Sinus Bradycardia	7 (0.4)	Myocardial Ischaemia	1 (0.1)
Palpitations	5 (0.3)	Sick Sinus Syndrome	1 (0.1)
Angina Pectoris	5 (0.3)	Supraventricular	1 (0.1)

MedDRA System Organ Class Preferred Term	Total Perampanel[a] N=1639 n (%)	MedDRA System Organ Class Preferred Term	Total Perampanel[a] N=1639 n (%)
		Tachycardia	
Tachycardia	4 (0.2)	Tachycardia Paroxysmal	1 (0.1)
Atrioventricular Block First Degree	4 (0.2)	Ventricular Arrhythmia	1 (0.1)
Atrial Fibrillation	3 (0.2)	Investigations	20 (1.2)
Conduction Disorder	2 (0.1)	ECG Abnormal	4 (0.2)
Acute Coronary Syndrome	1 (0.1)	ECG QT Prolonged	4 (0.2)
Angina Unstable	1 (0.1)	Blood Pressure Diastolic Decreased	3 (0.2)
Arrhythmia	1 (0.1)	ECG T Wave Abnormal	2 (0.1)
Atrial Flutter	1 (0.1)	Heart Rate Decreased	2 (0.1)
Atrioventricular Dissociation	1 (0.1)	ECG QRS Complex Prolonged	1 (0.1)
Bradyarrhythmia	1 (0.1)	ECG Normal	1 (0.1)
Bundle Branch Block Left	1 (0.1)	ECG QT Shortened	1 (0.1)
Cardiac Arrest	1 (0.1)	ECG ST Segment Elevation	1 (0.1)
Cardiac Hypertrophy	1 (0.1)	ECG ST-T Segment Abnormal	1 (0.1)
Coronary Artery Disease	1 (0.1)	Heart Rate Increased	1 (0.1)
Coronary Artery Stenosis	1 (0.1)	Heart Rate Irregular	1 (0.1)
Dilatation Atrial	1 (0.1)		

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period. Subject with two or more adverse events with the same preferred term is counted only once for that preferred term. [a]: Subjects treated with perampanel in any study.

Electrolytes

Markedly abnormally low sodium values occurred in 12 (2.8%) subjects in the placebo group and 25 (2.5%) subjects in the total perampanel group. Across the perampanel dose groups, the values ranged from 1.1% to 4.9%, with the highest value in the 12 mg/day

group. All of these subjects were taking at least one concomitant AED known to cause decreases in sodium, that is, carbamazepine, oxcarbazepine or valproic acid. When the analysis was limited to subjects with normal baseline values for sodium, markedly abnormal low values during treatment occurred in nine (2.2%) of the subjects in the placebo group and 15 (1.5%) of those in the total perampanel group.

Markedly abnormally high values occurred in 2 (0.5%) subjects in the placebo group and 10 (1.0%) subjects in the total perampanel group. Across the perampanel dose groups, the values ranged from 0% to 2.8%, with the highest value in the 4 mg/day group.

None were SAEs. Discontinuations were due to blood bicarbonate decreased, blood creatine phosphokinase increased, blood potassium decreased and blood sodium decreased (1 subject each in the perampanel group).

In the epilepsy all treated pool, AEs related to electrolytes or other chemistry parameters each occurred in ≤ 2.6% of the subjects. There were 3 SAEs: hyponaetraemia in 2 subjects and hypochloremia in 1 subject. The only discontinuations were blood bicarbonate decreased, blood creatine phosphokinase increased, blood potassium decreased and blood sodium decreased (one subject each).

Evaluator's conclusions on safety

The risks common in the Healthy subjects (dizziness, somnolence, headache, fatigue, and nausea) were also common in the epilepsy subjects.

AEs related to alertness and cognition occurred in 10 (8.6%) of the subjects on placebo and 122 (35.6%) of those in on perampanel.

Cardiac disorders and ECG related AEs occurred in 11 (3.2%) of those in the multi-dose total perampanel group but not placebo.

Falls occurred in two (1.7%) subjects in the placebo group and 18 (5.2%) subjects in the total perampanel group (four in the > 4 to 8 mg/day group and 14 in the > 8 to 12 mg/day group).

In the Epilepsy Phase III Double-blind Pool very common AEs (dizziness, somnolence, fatigue, irritability and fall) were at least twice as common with perampanel 8 mg/day as placebo (the exception was headache with similar incidence) and the incidence increased with 12 mg/day.

On 8 mg/day perampanel among the common AEs nausea, weight increased, vertigo, ataxia, gait disturbance and balance disorder were at least twice as common as with placebo.

In relation to the Elderly (> 65) there were only 31 of 1639 subjects in the Epilepsy All Treated Pool and only 20 in the Epilepsy Phase III Double-blind Pool (of whom 26 received ≥ 8 mg/day). Not only was there a higher incidence of any AEs in the elderly but some of concern were much higher for example dizziness and fall. The sponsor claims a much more extensive population exposed in non-epilepsy trials, however, of elderly patients in one group of trials there were only 39 who received >4 to 8 mg/day and of elderly in another group of trials while there were 133 receiving the >4 to 8 mg/day, none of the elderly in either trial indication group received >8 mg/day.

Adolescents: In the Epilepsy Phase III Double-blind Studies 72/77 (93.5%) adolescents on perampanel completed compared with 37/45 (82.2) on placebo, with 2 (2.0%) and 3 (6.7%) discontinued respectively due to an AE. On the data provided there appeared to be some differences in the nature of the more common AEs compared with adults.

First round benefit-risk assessment

First round assessment of benefits

The benefits of perampanel in the proposed all partial-onset seizures with or without secondarily generalised seizures are:

- A novel type of anticonvulsant.
- Not all the median or mean results for ≥ 4 mg OD treatment groups in the pivotal studies achieved the 20% separation in percent change in seizure frequency per 28 days, however there was consistent statistically significant difference shown by the p values.
- With the responder rate; Study 304 failed to show any statistically significance from placebo for either 8 or 12 mg while Study 305 did with differences from placebo approaching 20%; Study 306 showed for 4 and 8 mg groups statistically significant differences from placebo approaching 20% for the 8 mg group.
- Studies 304 and 305 showed, for patients with secondarily generalised seizures, statistically significant differences > 20 % from placebo in both percent change in seizure frequency per 28 days and responder rate, while Study 306 could show no significant difference in either.
- There are relatively few discontinuations in the long term studies in the group on a maximum of > 8 to 12 mg/day (73.3%) with most discontinuations due to AEs (103/297 34.7%).
- The mean Percent Change from Pre perampanel in Seizure Frequency per 28 Days and the Responder Rate was maintained among those continuing on the drug.
- Subjects who completed the double-blind studies at a dose of 8 mg and then increased their dose to 12 mg in the Open label extension Maintenance Phase showed that the 50% responder rate rose from 38.5% on a dose of 8 mg to 48.3% in the same subjects on a dose of 12 mg. However overall the results for the 12 mg group were less than the 8 mg group.

First round assessment of risks

The risks of perampanel in the proposed usage are:

- In the Phase III Double-blind Studies only 58 adolescents were on ≥ 4 mg/day of perampanel. There were 124 adolescents enrolled in the trials with descriptive summary results only; a study in adolescents was ongoing at the time of submission. There were thus relatively few adolescents on the proposed dosage and the AE profile has some differences with a greater incidence of somnolence and aggression.
- There were only 31 Elderly (> 65) of 1639 subjects in the Epilepsy All Treated Pool and only 20 in the Epilepsy Phase III Double blind Pool (of who 26 received ≥ 8 mg/day). The sponsor argues that since 1324 Elderly (> 65y) were treated in non-epilepsy trials that safety data is adequate, however what data there is for > 65 year old epilepsy patients suggests a higher incidence of AEs than in other adults, and in actuality only 169 elderly in non-epilepsy trials received > 4 to 8 mg/day and none received >8 mg/day.

First round assessment of benefit-risk balance

The risk benefit balance for the proposed indication was considered unfavourable by the clinical evaluator.

The risk benefit balance could be considered favourable if the indication is modified as recommended below.

First round recommendation regarding authorisation

Many of the summary tables referred to in the sponsor's Summary of Clinical Efficacy and sponsor's Summary of Clinical Safety were not included in the submission. The sponsor was asked to submit all referenced supporting tables. These confirmed the very small numbers involved in elderly and adolescent patients treated for the disease at the recommended dosage.

It is recommended that Fycompa not be approved for the Indication requested.

It is recommended that Fycompa be registered for:

> *For the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in adult patients with epilepsy aged < 65years.*

Clinical questions

Pharmacokinetics

Question 1

In the company study report of Study E2007-A001-040, the sponsor stated: "The percentage of AUC_{0-inf} obtained by extrapolation was greater than 20% in 77 of 99 profiles in total".

'Total' in this context refers to the combined percentage of AUC_{0-inf} for the a) 12 mg perampanel tablet and b) the 6 times 2 mg perampanel tablets. AUC_{0-t} should cover at least 80% of AUC_{0-inf}[21].

What proportion of AUC_{0-inf} was covered by AUC_{0-t} for the a) 12 mg perampanel tablet and b) the 6x2 mg perampanel tablets?

Question 2

Where in the study report for drug interaction (ketoconazole) study, E2007-E044-005, are the results for the determination of any cross-over effects between Treatment Periods 1 and 2?

Question 3

In the calculation of primary and secondary PK parameters in Study E2007-A001-014, and the subsequent log ratios between midazolam alone and midazolam in combination of perampanel at steady-state, the sponsor used arithmetic means in Table 9 Company Study Report (CSR) [not in AusPAR] instead of geometric means. Geometric LS means ratios and their 90% confidence intervals were calculated in the other drug-drug interaction studies submitted in this application.

What are the geometric LS means ratios and their 90% confidence intervals for the primary PK endpoints in Study E2007-A001-014?

Question 4

In Study E2007-E044-025, urine was collected for 24 hours after the last dose of perampanel (Day 20) for metabolite identification purposes.

[21] EU adopted guideline: CPMP/EWP/QWP/1401/98 Rev.1/Corr 20 January 2010

Where in this report are the results of this urinalysis and were any metabolites identified?

Question 5

Where in the clinical study report for the abuse potential study, E2007-A001-024, are the results for the determination of any cross-over effects between treatment sequences for each investigational product?

Second round evaluation of clinical data submitted in response to questions

The evaluator's comments on the sponsor's responses to the *Clinical questions* listed above are detailed in Attachment 2.

Second round benefit-risk assessment

The sponsor's response has not altered the risk benefit decision given under *First Round Benefit-Risk Assessment*.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 1.5 (dated 22/05/2012, DLP 01/12/2010) and Australian Specific Annex (dated March 2013, data lock point (DLP) not given) which were reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 13.

Table 13. Important identified and potential risks and missing information.

Important identified risks	Dizziness
	Somnolence
	Aggression
	Balance disorder, ataxia, and falls (particularly in the elderly)
	Interaction with levonorgestrel-containing contraceptives, and unintended pregnancy exposures
	Weight gain
	Blurred Vision
Important potential risks	Suicidality
	Drug abuse, misuse, dependency and withdrawal
	Off-label usage
	Skin photosensitivity
Important missing information	Use in patients <12 years of age
	Impact on cognition and growth in the pediatric population.
	Long term safety in adolescents and adults
	Use in human pregnancy and lactation
	Long term effects of perampanel binding to elastin, melanin and hepatic cells
	Use in patients with cardiovascular disease, hypertension, congestive heart failure, history of myocardial infarction or any evidence of risk factors for QT prolongation
	Use in patients with a history of psychotic disorder or suicidal behaviour in the previous 2 years
	Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease
	Use in patients with a history of drug or alcohol dependency
	Use in patients who are taking vigabatrin
	Use in patients with clinically significant renal or respiratory disease
	Idiosyncratic reactions related to reactive metabolites
	Use in the elderly with epilepsy, with particular monitoring of dizziness, balance disorders and falls
	Non CYP3A drug-drug interactions

Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, the following recommendations are made.

There were two reports of homicidal ideation in the literature[22,23,24] which were sourced from Studies E2007-G000-307 and E2007-G000-304. The sponsor has not included these cases in the submitted RMP. Furthermore, there were additional reports reviewed by the FDA that may not have been coded as 'homicidal ideation' but involved patients with homicidal ideation, as outlined in case narratives. As a result, 'homicidal ideation' should be added as an Important Potential Risk and cases should be reported through Periodic Safety Update Report (PSUR) updates.

The term 'psychiatric reaction' (or an equivalent term) should be added as an Important Identified Risk to include adverse events not captured by the Ongoing Safety Concerns 'aggression' and 'homicidal ideation', such as anger, hostility, irritability and behaviour change.

'Tendon/ligament rupture' should be added as an Important Potential Risk and cases should be reported through PSUR updates.

'Cholelithiasis and pancreatitis' should be added as an Important Potential Risk and cases should be reported through PSUR updates.

Contents of the Pharmacovigilance submission

The sponsor proposes routine and additional pharmacovigilance activities.

The sponsor proposes routine risk minimisation activities for important identified risk, important potential risks and missing information.

The presentation of the written submission is considered acceptable with some deficiencies. The Australian Specific Annex (ASA) does not include a summary table of the risk minimisation plan. As a result the summary table of the risk minimisation plan from the EU RMP was used in this report.

Summary of recommendations

It is considered that the sponsor's response to the TGA's request for further information did not adequately addressed any of the issues identified in the First Round RMP evaluation report. The First Round recommendations and additional recommendations are summarised below.

Additional recommendations

Recommendations concerning the sponsor's proposed ongoing safety concerns

The Ongoing Safety Concern 'psychiatric reaction' should incorporate psychosis.

'Manifestations of low impulse control' (or an equivalent term) should be added as an Ongoing Safety Concern.

Recommendations concerning the sponsor's proposed risk minimisation activities

For details of recommended amendments see *Summary of outstanding issues, Recommendations concerning the sponsor's proposed risk minimisation activities* below.

[22]Faulkner MA, Burke RA 2013. Safety profile of two novel antiepileptic agents approved for the treatment of refractory partial seizures: ezogabine (retigabine) and perampanel. *Expert Opin Drug Saf* Jul 25 [Epub ahead of print].
[23]Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, Squillacote D, Yang H, Gee M, Zhu J, Laurenza A 2013. Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia* 54(1):126–34.
[24]Serratosa JM, Villanueva V, Kerling F, Kasper BS 2013. Safety and tolerability of perampanel: a review of clinical trial data. *Acta Neurol Scand* 127(Suppl 197):30–35.

Summary of outstanding issues

Further safety considerations

The sponsor should be aware that safety considerations may be raised by the nonclinical evaluator or the Nonclinical Evaluation Report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations concerning the sponsor's proposed ongoing safety concerns

1. 'Homicidal ideation' should be added as an Important Potential Risk and cases should be reported through PSUR updates.
2. The term 'psychiatric reaction' (or an equivalent term) should be added as an Important Identified Risk to include adverse events not captured by the Ongoing Safety Concerns 'aggression' and 'homicidal ideation', such as anger, hostility, irritability, behaviour change, and psychosis.
3. 'Tendon/ligament rupture' should be added as an Important Potential Risk and cases should be reported through PSUR updates.
4. 'Cholelithiasis and pancreatitis' should be added as an Important Potential Risk and cases should be reported through PSUR updates.

Recommendations concerning the sponsor's proposed pharmacovigilance activities

The sponsor is advised to either include the Ongoing Safety Concerns 'Use in patients with clinically significant renal or respiratory disease' and 'Use in patients with hepatic insufficiency whether related to concomitant medications or underlying liver disease' in study E2007-G000-402, or conduct other relevant additional pharmacovigilance activities to address these Ongoing Safety Concerns.

1. The sponsor should provide details of the proposed expected reports for the pregnancy registry.
2. The sponsor should provide final reports of the studies to investigate non CYP3A drug-drug interactions as soon as they become available.
3. It is noted that, in the proposed PI, the sponsor states that phenobarbital (a barbiturate) and clonazepam (a benzodiazepine) have no influence on perampanel concentration and vice versa. Given the likely concomitant use of central nervous system (CNS) depressants with perampanel, the sponsor should specify from where this information was obtained.

Recommendations concerning the potential for medication errors

1. The sponsor should align the EU and Australian colour scheme used for different tablet strengths.

Recommendations concerning the risk minimisation activities proposed by the sponsor

1. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:
    a. In the 'Precautions' section, the PI should include a statement on psychiatric events (anger, hostility, irritability and behaviour change) in patients treated with perampanel, in particular in patients with existing psychiatric illness, in

adolescent patients, at higher doses, and in the titration phase to a higher dose (or a statement to that effect).

b. In the 'Precautions' section, the PI should include a statement that perampanel has the potential to exacerbate pre-existing conditions, including poor impulse control and other behavioural disorders (or a statement to that effect).

c. In the 'Precautions' section, the PI should, under a separate heading, include a statement on homicidal ideation in patients treated with perampanel, in particular in patients with existing psychiatric illness, and in particular at higher doses or in the titration phase to a higher dose (or a statement to that effect). This information should be based on the case reports of homicidal ideation.

d. In the 'Precautions' section, the PI should, under the 'Suicidal Ideation' and 'Homicidal ideation' headings include the need for prescribers to specifically ask patients about suicidal and homicidal thoughts before and during therapy with perampanel (or a statement to that effect).

e. In the 'Precautions' section, the PI should include a statement that careful monitoring and appropriate dose adjustments are necessary to sufficiently mitigate the risks of psychiatric adverse reactions, in particular in patients with existing psychiatric illness (or a statement to that effect).

f. In the 'Precautions' section, the PI should include the need for prescribers to specifically alert patients to the risk of lack of insight that may be associated with perampanel therapy (or a statement to that effect).

g. In the 'Precautions' section, the existing statement on abuse potential should be strengthened, that is, the heading should be expanded to 'Abuse potential and dependence' and under that heading, statements that tolerance, and physical and psychological dependence may occur with perampanel treatment should be included (or statements to that effect). These statements should include meaningful information from the definitive abuse liability study (Study E2007-A001-024).

h. In the 'Precautions' section, the PI should include a statement that in adolescent patients, elderly patients, and existing psychiatric illness, careful consideration of the benefit versus the risk of perampanel treatment should occur (or a statement to that effect).

i. In the 'Precautions' section, the PI should include a statement that more adverse events occur in the elderly, including adverse events more significant for the elderly, such as dizziness or falls (or a statement to that effect).

j. In the 'Precautions' section, the PI should include a statement that adolescents are more likely to be exhibiting aggression or similar behaviour than adults (or a statement to that effect).

k. In the 'Precautions' section, the PI should include a pregnancy category (to be determined in conjunction with the Non-clinical evaluator).

l. In the 'Adverse Events' section, the PI should include a separate paragraph on weight gain observed in clinical trials and that weight should be monitored in patients treated with perampanel (or a statement to that effect).

m. In the 'Dosage and Administration' section, the PI should contain a statement that the lowest dose possible that controls epilepsy symptoms should be used to minimise adverse events, in particular in the elderly, in adolescents, and in patients with existing psychiatric illness (or a statement to that effect).

2. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to accommodate the changes made to the product information document.
3. A prescriber guide and checklist as well as patient education materials should be developed as additional risk minimisation activities. Due to their importance, it is recommended to the Delegate that additional risk minimisation activities acceptable to the TGA are imposed as a condition of registration for this product.

The sponsor should provide the TGA with the following details for agreement:

· All draft education materials;

· A clear distribution plan; and

· A clear plan to measure the effectiveness of the additional risk minimisation activities.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM) (summary)

Lack of data

The sponsor should provide evidence that 'phenobarbital (a barbiturate) and clonazepam (a benzodiazepine) have no influence on perampanel concentration and vice versa'.

There seems to be a lack of data on patients with a history of mental illness or safe use in people with history of psychotic disorders or suicidal behaviour in the previous 2 years and in patients with a history of drug or alcohol dependency. Patients with epilepsy, particularly those with epilepsy secondary to organic brain damage, often have low impulse control.

PI recommendations

The PI should include a warning regarding homicidal ideation, consistent with the warnings for other antiepileptic medications.

The PI should include the potential exacerbation of pre-existing conditions, including poor impulse control and other behavioural disorders.

The PI should encourage prescribers to specifically ask patients about suicidal and homicidal thoughts consider the potential lack of insight and make patients aware of this risk at the time of prescribing. The PI should include information specifically based on the case reports of the adverse events which had occurred.

ACSOM advised that a black box may not be appropriate in the Australian context.

Key changes to the updated RMP

Not applicable.

Additional risk minimisation activities for Australia

Table 14. Routine risk minimization activities

Important Identified Risks	
Psychiatric Reaction	To be monitored and reported via PSURs
Important Potential Risks	
Homicidal ideation	To be monitored and reported via PSURs
Tendon/Ligament rupture	To be monitored and reported via PSURs
Cholelithiasis and pancreatitis	To be monitored and reported via PSURs

Additional risk minimisation activities

Additional risk minimisation activities will include

- Prescriber guide and checklist
- Patient education materials

These will be prepared and regularly reviewed to reflect in market use, and will be subject to TGA Office of Product Review approval prior to approval /use.

Suggested wording for conditions of registration

RMP

The implementation of EU-RMP Version 1.5 (dated 22 May 2012, data lock point (DLP) 01 December 2010 and Australian Specific Annex (dated May 2014), and any future updates (where TGA approved) for Perampanel (Fycompa).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections to approval on quality/biopharmaceutics grounds.

The initial chemistry evaluator noted that contradictory information relating to presentation of the quantity of active ingredient in the initially submitted dossier. This has been resolved and the product will now be referred to as perampanel (as hemisesquihydrate) when expressing the quantitative composition of the active moiety. This is in accordance with the 2009 EC guidance document A Guideline on Summary of Product Characteristics states that '*where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass units of the active moiety (base, acid or anhydrous material), e.g. '60 mg toremifene (as citrate)' or toremifene citrate equivalent to 60 mg toremifene*'.

Nonclinical

There were no objections to approval on nonclinical grounds.

The nonclinical evaluator noted that perampanel was active in various seizure models (intracerebroventricular AMPA-induced, audiogenic, maximal electroshock, PTZ-induced) in mice and in kindling models in mice and rats, with no effect in the GAERS model in rats. In addition perampanel showed dose-dependent anti-allodynic effects in rat models, beneficial effects in EAE rodent models of multiple sclerosis, and generally enhanced the effect of L-DOPA in rat and primate models of Parkinson's disease.

The nonclinical evaluator considered there is reasonable supporting nonclinical evidence that perampanel is a potent, selective, non-competitive AMPA-type glutamate receptor antagonist. Issues arising from the nonclinical evaluation are listed below:

1. Systemic exposures achieved in the animal studies of long-term toxicity, carcinogenicity and reproductive toxicity were generally less than anticipated clinical exposure due to dose-limiting clinical toxicity, and target organs of toxicity have not been identified. Rodent carcinogenicity studies were negative, although exposures achieved were less than clinical exposure. Adequate genotoxicity testing was negative.
2. The adequate safety margin in a hERG in vitro assay suggested only a low QT prolongation liability, but in vivo nonclinical confirmation was limited (low exposure) and clinical confirmation will be required.
3. The clinical significance of the prolonged residence time of drug related material in aorta and eyeball is unknown. Medicines which accumulate in aorta can have cardiovascular toxicity (for example, rofecoxib).
4. In view of the visceral abnormality (diverticulum of the intestine) in 1 of 2 rat embryofetal development studies, a pregnancy Category of B3 is considered prudent at this stage (B1 was proposed by the sponsor).
5. A possible dependence liability has been noted in animal studies.

Clinical

Pharmacology

Following oral administration, perampanel was rapidly absorbed, with the mean T_{max} ranging from 0.5 to 4.0 hours. Food reduced the C_{max} and increased T_{max} but did not significantly alter the AUC for perampanel. T_{max} was delayed by 2 to 3 hours compared to T_{max} fasted. Bioavailability is high with studies suggesting perampanel is almost completely absorbed. Volume of distribution (Vd) varied directly with BMI. In a subject with a BMI of 26kg/m^2 the Vd was estimated at 89.6L. Protein binding in humans is high at 95.3% to 95.8%. Perampanel is primarily bound to human serum albumin and α1-acid glycoprotein, and partially bound to γ-globulin.

The elimination half-life of perampanel is about 105 hours, so that steady state is reached in about 2 to 3 weeks. Pharmacokinetics is linear within the dose range on single and multiple dosing. With doses above 12 mg, C_{max} was slightly less than proportional. In healthy adult poly-drug users there was a trend towards dose-proportionality from 8 to 36mg/day perampanel in AUC indices but not in C_{max}. In healthy subjects given once daily doses from 1 mg to 6 mg, mean AUC accumulation ratios varied between 3.40 and 4.88. Age, body weight, sex and race did not influence PK parameters to a clinically significant extent.

The main metabolic pathway of perampanel is primary oxidation mediated by CYP3A4 and/or CYP3A5. Multiple oxidated metabolites are produced. Following metabolic

conversion to glucuronides, subsequent clearance is rapid and predominantly faecal (approximately 70%). Active biliary excretion of oxidative metabolites occurs. In faeces M1 + M4 are the predominant metabolites accounting for 43% of recovered radioactivity in a mass balance study. M7 and unchanged perampanel accounted for 15% and 10% of radioactivity in faeces, respectively. The remaining radioactivity in faeces consisted of M2, M3, M5, M15 and M35. Excretion of glucuronide metabolites of these compounds occurs in urine and accounted for about 30% of recovered radioactivity in a mass balance study. Negligible perampanel is excreted unchanged in urine.

Dose adjustment, including slower dose titration for patients with mild to moderate impairment of hepatic function has been recommended on the basis of results from a single dose study described in the CER. Perampanel is not recommended for patients with severe impairment of hepatic function. No studies were conducted in patients with renal impairment. The sponsor has proposed that perampanel not be recommended for patients with severe renal impairment, including those receiving dialysis.

Specific interaction studies were performed with carbamazepine, ketoconazole, oral contraceptives (OCs), midazolam and levodopa and further data on interaction potential were provided in the population pharmacokinetics (PopPK) analysis of Phase III study data. Of most clinical significance, carbamazepine increased apparent oral clearance of perampanel 3 times with a corresponding decrease in C_{max} and $AUC_{o\text{-}inf}$ by 26% and 67%, respectively. Perampanel was associated with a reduction in C_{max} and $AUC_{(0\text{-}24h)}$ for levonorgestrel with each decreased by approximately 40%.

Pharmacodynamic studies showed dose related sedation and impairment of motor function which resolved within 2 weeks of ceasing perampanel. These effects were additive to those of alcohol. Of most significance was the abuse potential study (024 described in the CER). In this study the likeability of perampanel was compared with ketamine 100 mg and alprazolam 1.5 mg and 3 mg in 40 current recreational polydrug users. Positive effects were measured using the Addiction Research Center Inventory (ARCI) Morphine Benzedrine Group (MBG) scale, a 0 to 16 point scale where 16 = euphoria. Perampanel had median Addiction Research Center Inventory (ARCI)-Morphine Benzedrine Group (MBG) scores that were dose related and, at the highest dose tested (3 times proposed maximum proposed dose), time weighed mean and median ARCI-MBG scores were higher than that of ketamine as indicated in the table below extracted from the study report.

Table 15. Descriptive Statistics of Derived Endpoints for ARCI MBGa– Pharmacodynamic Analysis Set

Endpoint/ Statistic	Placebo	Perampanel			Ketamine	Alprazolam	
		8 mg	24 mg	36 mg	100 mg	1.5 mg	3 mg
E_{max}							
Mean	2.8	5.6	9.4	10.0	10.3	7.8	10.2
SD	3.5	4.27	5.16	5.51	4.15	4.62	4.3
Median	2.0	5.0	10.5	12.0	11.5	7.0	11.0
$TWmean_{(0\text{-}24h)}$							
Mean	1.7	2.0	3.4	4.5	2.4	2.5	3.7
SD	2.1	2.19	3.24	4.39	2.4	2.6	2.94
Median	1.0	1.1	2.7	2.5	1.5	1.6	2.4

ARCI=Addiction Research Center Inventory; E_{max}=Maximum effect; MBG=Morphine Benzedrine Group; SD=Standard deviation; $TWmean_{(0\text{-}24h)}$=Time-weighted mean from 0 to 24 hours postdose.

[a] Responses range from 0 to 16 (euphoria).

Sedative effects were measured using the ARCI Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale, a 0 to 15 point scale with maximum sedation scoring 15. This was a co-primary variable in Study 024.

Table 16. Descriptive Statistics of Derived Endpoints for ARCI PCAGa – Pharmacodynamic Analysis Set

Endpoint/ Statistic	Placebo	Perampanel			Ketamine	Alprazolam	
		8 mg	24 mg	36 mg	100 mg	1.5 mg	3 mg
E_{max}							
Mean	4.3	8.1	11.7	12.3	7.8	11.2	12.1
SD	3.08	3.93	2.83	2.30	3.50	2.64	2.07
Median	4.0	9.5	13.0	12.5	8.5	11.0	12.0
$TWmean_{(0-24h)}$							
Mean	2.9	4.0	7.3	8.7	3.4	5.1	6.3
SD	1.47	1.79	2.95	3.07	1.42	1.84	2.11
Median	3.0	4.0	7.5	9.5	3.3	5.0	6.1

ARCI=Addiction Research Center Inventory; E_{max}=Maximum effect; PCAG=Pentobarbital Chlorpromazine Alcohol Group; SD=Standard deviation; $TWmean_{(0-24h)}$=Time-weighted mean from 0 to 24 hours postdose.

[a] Responses range from 0 to 15 (sedation).

In this study propensity to take perampanel again was examined using a " Take Drug Again" visual analog scale (VAS) which provided a measure of the balance of drug effects and indicated willingness to take the drug again.

Table 17. Descriptive Statistics (Mean [Median]) of Derived Endpoints for Secondary Balance of Effects Measures – Pharmacodynamic Analysis Set

Measure/ Endpoint	Placebo	Perampanel			Ketamine	Alprazolam	
		8 mg	24 mg	36 mg	100 mg	1.5 mg	3 mg
Overall Drug Liking VAS[a]							
E_{max}	54.1 (51.0)	61.6 (59.5)	67.7 (68.0)	67.9 (74.0)	80.9 (87.0)	74.5 (73.5)	77.1 (77.5)
E_{min}	49.6 (50.0)	52.3 (50.0)	54.4 (51.0)	50.8 (51.5)	70.7 (74.0)	63.9 (64.5)	59.2 (63.5)
Mean[b]	51.2 (50.0)	57.7 (54.8)	61.3 (64.5)	57.6 (63.0)	77.1 (81.3)	69.8 (68.8)	69.5 (69.0)
Take Drug Again VAS[c]							
E_{max}	42.9 (50.0)	62.1 (59.0)	64.9 (71.0)	64.3 (70.5)	81.9 (96.0)	77.8 (77.0)	75.4 (78.0)
Mean[b]	36.9 (50.0)	57.7 (55.8)	59.8 (67.5)	56.2 (64.8)	77.5 (86.3)	70.8 (69.3)	70.1 (70.3)

E_{max}=Maximum effect; E_{min}=Minimum effect; VAS=Visual analogue scale.

[a] "Overall, my liking for this drug is", where responses range from 0 (Strong disliking) to 100 (Strong liking).

[b] Mean of 12, 24, and 48 hours postdose.

[c] "I would take this drug again", where responses range from 0 (Definitely not) to 100 (Definitely so).

For each dose of perampanel tested, both the overall liking and stated preference to take the drug again were lower for perampanel than for ketamine or either dose of alprazolam.

The sponsor also submitted an abuse potential evaluation report. The conclusions were organised according to the 8 factors listed in the Controlled Substances Act (CSA) in The United States and are further summarised below:

Factor 1: Actual or relative potential for abuse:

Perampanel showed no binding to known abuse related molecular targets including opioid receptors, serotonin (5-HT) and dopamine transporters and receptors, NMDA, gamma-aminobutyric acid (GABA), nicotinic acetylcholine or cannabinoid receptors.

The sponsor concluded from Study 024 that perampanel produced positive effects that were comparable to alprazolam, both in magnitude of effect, onset of action, and duration of effect. However, perampanel produced negative effects that were higher than alprazolam, and which lasted longer. On the "Take Drug Again" visual analogue scale, measuring the subject's desire to take the drug again, all doses of perampanel produced lower scores than 1.5 and 3 mg alprazolam, and most of the differences were statistically

significant. All doses of perampanel produced peak scores significantly lower than ketamine.

Factor 2: Scientific evidence of pharmacological effect:

The sponsor claimed the long half-life would be predicted to reduce withdrawal symptoms and repeated self-administration of the drug.

Factor 3: Other scientific knowledge regarding the drug:

Perampanel is not structurally similar to any Controlled Substances Act (CSA) scheduled drug. Also, there is no meaningful structural similarity between perampanel and the seven commonly used scheduled antiepileptic drugs (clonazepam, clorazepate, diazepam, lacosamide, lorazepam, phenobarbital, and pregabalin), or to phenyclidine, ketamine, or fentanyl.

The sponsor claimed a series of studies conducted to assess the tamperability of the drug product suggests that the most simple extraction methods for injection (that is, crushing the tablet and extracting in water) would not be viable due to the low solubility of the drug. Perampanel can be solubilised in other solvents.

Factor 4: Its history and pattern of abuse:

Data from the Drug Abuse Warning Network generally suggest that anticonvulsive drugs, as a class, are associated with fewer abuse related emergency department visits relative to several other classes of psychotropic drugs including antidepressants and muscle relaxers, most of which are unscheduled, and are generally regarded as having relatively low abuse potential.

Factor 5: Duration, scope and significance of abuse:

Based primarily on prescription for treatment of epilepsy and the abuse potential study results the sponsor predicted there may be some experimentation with perampanel but would not predict sustained abuse.

Factor 6: Risk (if any) to the public health:

The sponsor noted that only 5 overdose cases resulted in serious adverse events requiring hospitalisation, and in each case, the symptoms resolved. Even extremely high doses of perampanel (that is, at least 200 mg in one case) did not result in a fatal overdose. This section concluded that overall, it is unlikely that perampanel is associated with a major risk to public health related to its abuse.

Factor 7: Its psychic or physiological dependence liability:

With available data thus far, there was no evidence of emergent withdrawal symptoms in these studies where perampanel dosing ended without tapering.

Factor 8: Whether the substance is an immediate precursor of a controlled substance:

Perampanel, the starting material, intermediates, and major metabolites are not viable chemical precursors to any known controlled substance.

Perampanel had no clinically significant effect on QT interval.

Efficacy

Three pivotal double-blind, placebo-controlled, dose-escalation, parallel-group studies to evaluate the efficacy and safety of perampanel given as adjunctive therapy in subjects with refractory partial seizures were performed. These studies are described in the CER. These studies used similar designs but different doses of perampanel and were designed to be pooled. In Study 306 subjects were given perampanel at doses of 2 mg, 4 mg, and 8 mg daily while in Studies 305 and 304 the perampanel doses were 8 mg and 12 mg daily.

The studies had a 6 week pre randomisation phase, in which subjects recorded seizures in a daily diary. Those who experienced the required minimum number of seizures despite receiving antiepileptic drugs (AEDs) then entered the double-blind phase and were randomly assigned to one of three treatment groups (placebo or one of 2 perampanel doses as described above). The double-blind phase consisted of a 6 week titration period followed by a 13 week maintenance period, during which the subjects continued to receive the doses they achieved at the end of the titration period. After the double-blind phase there was a 4 week follow-up phase or subjects continued to an open-label extension study.

These studies enrolled subjects aged from 12 years with a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures (ILAE, 1989). Diagnosis was established by clinical history and an electroencephalogram (EEG) that was consistent with localisation related epilepsy. Normal interictal EEGs were allowed provided that the subject met the other diagnosis criterion (that is, clinical history).

Study subjects were required to have a documented occurrence, based on a valid seizure diary, of five or more partial-onset seizures during the 6 week pre-randomisation phase (at least two partial seizures during each 3 week period) and no 25 day seizure free interval over this 6 week phase. Only simple partial seizures with motor signs, complex partial seizures and complex partial seizures with secondary generalization were counted toward this inclusion.

Study subjects were currently being treated with one, two or a maximum of three approved AEDs at stable doses for at least 21 days prior to Visit 1. In the case where a new AED regime was initiated for a subject, the dose must have been stable at least 49 days prior to Visit 1. Only one inducer AED (defined as carbamazepine, phenytoin, phenobarbital, or primidone) out of the maximum of three AEDs was allowed. Benzodiazepines used for epilepsy, anxiety or sleep disorders counted as one AED.

The primary endpoint was the percent change in seizure frequency per 28 days during treatment relative to baseline in the Intent-to-Treat (ITT) Population (last observation carried forward (LOCF)). Key secondary endpoints were:

- 50% responder rate, with responders defined as subjects who experienced a 50% or greater reduction in seizure frequency per 28 days in the Maintenance Period relative to the Pre-randomization Phase.
- percent change in complex partial plus secondarily generalized seizure frequency per 28 days during treatment relative to baseline.

In Study 304 there was a statistically significant difference for the primary endpoint, favouring perampanel for the 8 mg and 12 mg daily doses. The key secondary efficacy parameter of % change in seizure frequency compared to placebo was also statistically significant for each perampanel dose. Differences in the 50% responder rate did not separate from placebo for either dose but there was a trend towards higher response rates with perampanel. In Study 305 the same dose regimens of perampanel were compared with placebo. In that study the primary and both key secondary efficacy measures were statistically significantly superior to placebo for each dose of perampanel.

Study 306 had 4 arms (2 mg, 4 mg and 8 mg perampanel and placebo). In that study the 4 mg and 8 mg perampanel doses were statistically significantly superior to placebo for: % change in seizure frequency per 28 days during treatment relative to baseline; 50% responder rate; and % change in complex partial plus secondarily generalized seizure frequency per 28 days during treatment relative to baseline.

A combined analysis of the pivotal studies was performed with results presented in the CER. The median % change in seizure frequency from baseline to the end of the double-

blind period was -12.77 for placebo; -13.63 for 2 mg perampanel; -23.33 for 4 mg perampanel; -28.76 for 8 mg perampanel and -27.18 for 12 mg perampanel. Difference from placebo in 50% reduction in seizure frequency is presented for each perampanel dose in the CER. These were 1.3%, 9.2%, 16.0% and 15.7% for perampanel 2 mg, 4 mg, 8 mg and 12 mg respectively (full analysis set). Therefore the number needed to treat (NNT) with any dose of perampanel from 4 mg to 12 mg to achieve a 50% reduction in seizure frequency was 6.25 to 10.9. Subgroup analysis by age showed statistically significant reductions compared with placebo for age groups 12 to 18 years and ≥18 to ≤ 65 years.

Perampanel had similar efficacy in patients aged <18 years as shown in Table 70 of the CER however only 98 adolescents received active treatment across the 4 dose groups in the 3 pivotal studies so no firm conclusions can be reached concerning relative efficacy in adolescents versus older patients from that analysis. No major differences were apparent between sexes or races (White/Asian or Pacific Islander). Patients given concomitant AED enzyme inducers (carbamazepine, oxcarbamazepine and phenytoin) generally had smaller reductions in seizure frequency than those not given concomitant enzyme inducers. In that subgroup analysis reductions in mean seizure frequency were statistically significantly superior to placebo only for the placebo versus 8 mg perampanel comparison for the subgroup not taking any concomitant enzyme inducing AEDs. Reductions in seizure frequency commenced from Week 1 of treatment, well before steady state was reached. There was no statistical analysis of these differences at that time-point however this was used as a basis for the sponsors proposed titration schedule.

Differences from placebo in responder rates were higher at North American study sites than in European study sites for both the 8 mg and 12 mg doses with the difference in the range of 20% for the both 8 mg and 12 mg dose. Neither region showed substantial difference in response rates between the 8 and 12 mg doses. There was a greater mean reduction in seizure frequency in Central and South American study sites (-28.18%) than in European (-7.07%) or North American sites (-16.16%). Placebo responder rates also differed across geographic regions, being highest in Central and South America and lowest in Europe.

Safety

Data in this submission dated from before 1 December 2010. At that time 1639 subjects with epilepsy had received perampanel in double-blind Phase II and III studies and open-label extensions. The total exposure to perampanel in epilepsy studies was 82,629.0 subject-weeks. A total of 1147 subjects received perampanel for > 6 months, 703 subjects for > 1 year, and 95 subjects for > 2 years. For the 102 subjects who were 12 to < 17 years old, the overall exposure to perampanel was 5095.4 subjects-weeks and perampanel had been taken for > 6 months, > 1 year, and > 2 years by 72, 49 and 4 subjects, respectively.

An additional 2717 subjects with non-epilepsy indications (neuropathic pain, Parkinson's disease, Multiple Sclerosis, and migraine received perampanel in double-blind Phase II and III studies and open-label extension studies. The overall exposure to perampanel in these studies was 86,176.1 subject-weeks. A total of 1251 subjects received perampanel for > 6 months, 556 for > 1 year, and 66 subjects for > 2 years.

The primary support for the safety of perampanel for its proposed indication and dose range is from the 3 pivotal studies (304, 305 and 306), 5 Phase II studies and III open-label extension studies. In that study pool 4 adverse events that led to death occurred either during treatment or within 30 days after the last dose of treatment. No deaths were attributed to perampanel. The most frequently reported SAEs were those related to epilepsy: convulsion [n =2 4, 2.0%]; status epilepticus [n = 9, <1%]; epilepsy [n = 4, < 1%]; grand mal convulsion [n = 4, < 1%]; partial seizures with secondary generalization [n = 2,

< 1%]; and drug withdrawal convulsions [n = 1]). Other SAEs reported in 6 (0.5%) or more subjects were aggression (n = 10), psychotic disorder (n = 6) and suicidal ideation (n = 6).

There was a dose related increase in discontinuations due to adverse effects with discontinuation due to AEs reported for 4.8% of subjects given placebo and 6.7%, 2.9%, 7.7%, and 19.2% of the subjects given perampanel 2 mg, 4 mg, 8 mg, and 12 mg respectively in the double-blind pivotal studies. Table 87 in the CER shows AEs leading to discontinuation by dose. Of particular concern, 16 (6.3%) patients given perampanel 12 mg discontinued due to psychiatric adverse events. These included anger (1.6%) and aggression (1.6%). The next most frequent cause of discontinuation was nervous system events, most frequently dizziness which caused 4.3% of the 12 mg dose group to withdraw.

The most frequently reported treatment-emergent adverse events were dizziness, somnolence, headache, fatigue, irritability and falls. These events were all dose related. The incidence of each of these events by dose is displayed in the CER. Only 20 patients aged ≥ 65 years received perampanel in the epilepsy studies. Dizziness and falls were particularly frequent in this group. Dizziness occurred in 55.6% of elderly patients given the 8 mg dose and falls occurred in 57.1% given the 12 mg dose (Table 106 in the CER).

Less frequent adverse events that appear to be dose related include aggression, reported in 0.5% of patients given placebo and 3.5% given 12 mg perampanel in the double-blind, placebo pool of subjects. Aggression was more frequently reported in adolescents (7.8%). There was a suggestion that confusional state may be more frequent with perampanel than with placebo, being reported in 0.5% of subjects given placebo and 1.6% given 12 mg perampanel. Only subjects in the perampanel group (no subjects given placebo) had suicide attempts and overdoses in the Phase III epilepsy studies double-blind pool (n=1) and the non-epilepsy double-blind pool (n=2) but these numbers are low.

While the above results for aggression were reported in the safety summary it is apparent some additional analyses have been conducted. The Delegate noted that the US PI includes the following statements: In the controlled Phase III epilepsy clinical trials, hostility and aggression related adverse reactions occurred in 12% and 20% of patients randomised to receive Fycompa at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. Fycompa treated patients experienced more hostility and aggression related adverse reactions that were serious, severe, and led to dose reduction, interruption and discontinuation more frequently than placebo-treated patients.

Clinically significant weight gain (that is, >7% body weight (BW)) occurred in 14%, 15.3% and 15.4% of patients perampanel given 4 mg, 8 mg and 12 mg respectively compared with 7.1% given placebo (Table 94 of the CER).

Clinical evaluator's recommendation

The clinical evaluator recommended that Fycompa not be approved for the Indication requested.

The clinical evaluator recommended that Fycompa be registered for:

> *For the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in adult patients with epilepsy aged < 65years.*

Risk management plan

Negotiation of the RMP is ongoing. The RMP evaluator considered that as perampanel is a first in class new chemical entity with a potential for drug abuse, misuse and dependency,

and with many potential adverse events that require careful monitoring, a prescriber guide and checklist as well as patient education materials should be developed as additional risk minimisation activities. The RMP evaluator further recommended that additional risk minimisation activities acceptable to the TGA be imposed as a condition of registration.

The RMP evaluator requested the sponsor provide the TGA with the following details for agreement:

- All draft education materials;
- A clear distribution plan; and
- A clear plan to measure the effectiveness of the additional risk minimisation activities.

The RMP evaluator also recommended that the Safety Specification be amended to include "psychosis" and "manifestations of low impulse control" (or an equivalent term) as ongoing safety concerns. Changes to the draft PI to provide more information about the adverse effects of reduced impulse control, homicidal ideation, suicidal ideation, lack of insight and abuse potential were also requested.

This submission was referred to the ACSOM. In particular, the ACSOM noted that anger, hostility, irritability homicidal ideation, suicidal ideation and behaviour change are observed in patients treated with perampanel. That committee advised that in the cases which contained homicidal ideation or behaviour, including the four cases listed in the OPR RMP evaluation, the association with aggression was dose related and there was a 2 to 15 fold increase in this behaviour at the higher dose.

With regard to suicidality the ACSOM noted that coding omissions for suicidal ideation within narratives of cases of hostility and aggression resulted in the number of cases coded as suicidal ideation being underestimated. ACSOM noted that it was difficult to draw definitive conclusions based on the deaths which occurred among perampanel users. ACSOM also noted that epilepsy itself is a suicide risk, in that there is a high suicide rate among epilepsy patients which is associated with psychotic behaviours and psychic auras**.** ACSOM advised that while the 4 case reports of homicidal behaviour were of concern, there are general psychiatric side effects associated with all anti-epileptic medications. However, as perampanel is first-in-class, it was reasonable to be cautious. ACSOM advised that it would be appropriate to include a warning in the Product Information (PI) regarding homicidal ideation however such a warning should be consistent with the warnings in the PIs for other antiepileptic medications.

ACSOM advised that patients with a past history of psychotic disorders were a specific group of patients who may be at higher risk of having their illness exacerbated by perampanel. ACSOM was concerned that that there was a lack of data on patient history of mental illness in the studies presented.

ACSOM noted that patients with epilepsy, particularly those with epilepsy secondary to organic brain damage, have low impulse control. Pharmacologically, perampanel increases agitation, however the way this is expressed is not necessarily a factor of the drug but influenced by personality. ACSOM further noted the potential risks of suicide, drug abuse, dependency and withdrawal and psychosis, and expressed concern at the lack of evidence for the safe use in people with history of psychotic disorders or suicidal behaviour in the previous 2 years and in patients with a history of drug or alcohol dependency. ACSOM advised that the warning in the PI could be broadened to include the potential exacerbation of pre-existing conditions, including poor impulse control and other behavioural disorders.

ACSOM advised that a black box may not be appropriate in the Australian context, as other similar medications are not required to include a black box warning and it would be

difficult to justify that there is greater risk associated with perampanel. ACSOM advised that warnings in the PI for perampanel be consistent with those in the PIs of other epilepsy medications.

Risk-benefit analysis

Delegate's considerations

A major concern with perampanel is its potential for abuse/misuse and dependency. While scheduling is yet to be determined perampanel appears to have similar ability to produce euphoria as ketamine and alprazolam, both S8 medicines[25] however it has less likeability and substantially fewer polydrug users stated they would take it again compared to either ketamine or alprazolam. The effects associated with abuse potential (euphoria and sedation) are dose related. Perampanel also results in significant dose related sedation that is additive with alcohol.

Aggression, hostility, suicidality and impulse control are also of concern, particularly if perampanel is given to patients with pre-existing low impulse control. The safety of use in patients with psychotic disorders or current or past drug abuse is not clear. Revised words to indicate this concern have been proposed for the PI. While at this stage is does not appear that a boxed warning to highlight these potential safety issues is required, careful postmarket observation will be needed. The Product Information should appropriately disclose the extent of information known about use in these patients and the incidence of these events in clinical trials. The actual incidence of hostility and aggression related events in patients given perampanel in the Phase III studies is not clear given the different incidences reported by the sponsor and in the US PI. *The sponsor is requested to provide reasons for this difference.*

Both the PI and the RMP should appropriately recognise the abuse potential of perampanel and the healthcare professional education program should inform participants of the extent of risk as demonstrated in Study 024. The ACPM is requested to advise on whether this is appropriate and whether recommending that initial prescribing be performed by neurologists is likely to reduce exposure to perampanel of patients who are more susceptible to its serious side effects.

The ACSOM was concerned about use in adolescents aged from 12 to 16 years however safety and efficacy in this population have been adequately demonstrated and use in that population is approved in both the EU and USA.

Given its long half-life the antiepileptic effect of perampanel should be of slow onset. Once daily dosing is supported. The proposed titration schedule is adequately supported by the pharmacokinetic and clinical trial data. Withdrawal effects, particularly from doses above the maximum recommended daily dose have not been studied. The effect of relevant concomitant medicines has been adequately explored.

The efficacy studies were well designed and clearly demonstrated a minimal effective dose and a dose response for doses up to 8 mg daily. The extent of benefit is fairly modest with between 6.25 and 10.9 patients given perampanel achieving a 50% reduction in seizure frequency overall, depending on the dose given. A clear increase in benefit was not demonstrated with dose increases between 8 mg and 12 mg for the overall population however adverse events are generally dose related. The benefit/risk balance for the 12 mg daily dose appears to be unfavourable with the exception of patients taking concomitant CYP3A4 inducing AEDs. These medicines increase the metabolism of perampanel

[25] Schedules 8= Controlled Drug

substantially. The 12 mg dose may be justified in these patients as it would result in exposures similar to the 4 mg to 8 mg doses in patients not taking CYP3A4 inducing AEDs.

Only 31 patients aged ≥65 years participated in the epilepsy studies. The incidence of dizziness and falls in this age group was unacceptably high given the modest benefit overall from perampanel. At this stage the Delegate did not propose to approve perampanel for use in patients aged over 65 years.

Overall, given the modest benefit and adverse event profile of perampanel, the Delegate considers it is unlikely to be an adjunctive AED of first choice by most prescribers. Nevertheless it is reasonable to allow it to be considered as an adjunctive AED treatment subject to negotiation of a satisfactory Risk Management Plan.

Summary of issues

Perampanel has potential for abuse and misuse and has been referred to the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for consideration scheduling to S8. While the scheduling decision is not yet known consideration of additional measures to reduce abuse/misuse and dependency may be required. These are to include a comprehensive education program for prescribers and patients, monitoring and some degree of restriction of use in patients with a history of drug abuse or misuse.

The incidence of aggression and hostility associated with perampanel is unclear. The sponsor has been requested to provide clarification.

Efficacy, in terms of the proportion of patients with epilepsy who have a reduction in seizure frequency of ≥50% from baseline compared with placebo is modest at all doses with little evidence of increasing benefit with increasing dose.

The risk/benefit of the 12 mg dose for patients not taking concomitant medicines that increase the metabolism of perampanel appears to be negative, though comprehensive assessment of efficacy in this sub-group has not been performed.

Given the low numbers of elderly patients assessed and the high frequency of dizziness and falls in those patients the benefit/risk for perampanel does not appear to be favourable for this group.

Proposed action

The Delegate had no reason to say, at this time, that the application for Fycompa (perampanel) should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider initial prescribing should be limited to neurologists?
2. Does the committee consider the 12 mg dose should be restricted to patients taking concomitant strong CYP3A4 inducers?
3. Should the PI contain a statement to the effect that perampanel is not recommended in patients with a history of psychosis, low impulse control or drug abuse?
4. The benefit/risk balance for perampanel in patients aged ≥65 years appears to be unfavourable. The committee is requested to provide advice on the use of perampanel in this population group.
5. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

1. *Does the committee consider initial prescribing should be limited to neurologists?*

Eisai believes that the initiation of the treatment does not need to be restricted to neurologists.

Perampanel has been tested in almost 6,000 subjects for up to 6 years in a global program across all five continents and in over 40 countries. Perampanel has been approved in over 36 countries including EU, USA, Canada and Switzerland, and marketed to date in 15 of them, with an estimated exposure of almost 1.4 million patient days, and an overall safety profile similar to what was observed in the clinical program. Initial prescribing in all these countries is not limited to a neurologist.

The proposed PI provides sufficient guidance, for the assessment of the risk/benefit ratio, as well as on the dosing and administration in relevant subgroups of patients, which does not necessarily require a neurologist for the initial prescription.

Moreover, since perampanel would only be approved for adjunctive use, the initial evaluation, diagnosis, and treatment plan by a neurologist will already have been performed if needed. In addition many patients who have already been diagnosed with epilepsy may need additional treatment for inadequate control of the disease and are likely being followed by non-neurologists.

2. *Does the committee consider 12 mg dose should be restricted to patients taking concomitant strong CYP3A4 inducers?*

Eisai believes that the 10 mg and 12 mg doses are beneficial for a meaningful proportion of patients with and without concomitant enzyme inducing AEDs, including many of the most refractory ones. These are indeed important clinical options for these patients in their clinical armamentarium focused on achieving the goal of greater seizure reduction, (if not seizure freedom,) or decrease in severity of seizures in this group of patients.

These benefits were found regardless of background antiepileptic drug (AED) therapy, although refractory patients already taking AEDs that induce liver metabolism of perampanel (carbamazepine, oxcarbazepine, and phenytoin) have a higher likelihood of requiring higher doses of perampanel than subjects taking non-inducer AEDs.

These doses have been shown to be safe and efficacious and preferred in these patients, as illustrated in long term studies in which over 90% of study subjects, regardless of background AED therapy, were titrated to the 10 or 12 mg doses, with the proportion of subjects completing the core study at 8 mg achieving greater benefits when titrated up to 10mg and 12mg.

Table 18 (from the US Prescribing Information), below, shows a dose-dependent increase of the efficacy in both subgroups at doses up to 12mg, without and with inducers, although the effect is lower in the latter, consistent with the reduction in exposure.

Table 18. Median Treatment Effect (drug - placebo) for Combined Studies (Study 1, 2 and 3) Based on the Presence or Absence of Concomitant FYCOMPA Inducing AEDs (carbamazepine, oxcarbazepine, phenytoin)[a]

	Median Percent Reduction From Placebo		Responder Rate[b] (Drug – Placebo)	
	Without Inducers	With Inducers	Without Inducers	With Inducers
2 mg/day	8.2%	0.5%	6.3%	1.9%
4 mg/day	15.3%	11.9%	15.4%	8.1%
8 mg/day	25.7%	14.4%	28.2%	13.0%
12 mg/day	33.2%	19.2%	39.3%	12.3%

[a]Patients from Latin American region are excluded because of a significant treatment-by- region interaction due to high placebo response.
[b]The proportion of patients with at least a 50% decrease in seizure frequency

Moreover, efficacy data supported by PK/PD modelling indicate that clinically meaningful improvement in seizure control, regardless of background therapy, is observed with once-daily perampanel dosing with 4 mg and this benefit is enhanced as the dose is increased up to 12 mg/day. The slope for the relationship between seizure frequency and plasma concentrations associated with doses of 8 to 12 mg was not appreciably different from the slope for the relationship between seizure frequency and concentrations associated with doses of 4 to 8 mg, confirming that the incremental benefit of dose increases extends linearly throughout the proposed therapeutic dose range of 4 to12 mg/day. Results from the population PK/PD model found no differences in the relationship between perampanel concentration and seizure frequency as a function of gender, age, race, region, study or co-administered AEDs further supporting a general conclusion of improvement in seizure control with an increase in plasma perampanel exposure. As there is a large overlap in exposure due to inter-subject variability, which cannot be predicted in advance, a meaningful proportion of subjects on non-inducing AED would attain, and benefit from, 12 mg.

Eisai feels the current dosing instructions included in the proposed version of the PI (and as shown below) are consistent with the general approach for treating patients with partial onset seizures and epilepsy patients globally. The PI also describes groups of patients for whom 10 mg and 12 mg should not be considered (for example, patients with hepatic impairment) or should be considered with caution (for example, women on oral contraceptives containing levonorgestrel).

Treatment with Fycompa should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medications that do not shorten the half-life of perampanel see *Interactions with Other Medicines*) should be titrated no more frequently than at 2 week intervals. Patients who are taking concomitant medications that shorten the half-life of perampanel (see *Interactions with Other Medicines*) should be titrated no more frequently than at 1 week intervals.

In summary, Eisai's position is that there is a positive benefit/risk ratio for perampanel in the treatment of partial onset seizures, and the 12 mg dose may provide, at acceptable risk, additional benefit over 8 mg for a meaningful proportion of patients, including the ones on non-inducers. Eisai's position also identifies patients for whom the 12-mg dose is not recommended.

3. *Should the PI contain a statement to the effect that perampanel is not recommended in patients with a history of psychosis, low impulse control or drug abuse?*

History of psychosis

Suffering from active psychotic disorder(s) and/or unstable recurrent affective disorder(s) was an exclusion criterion in all epilepsy studies; however, subjects with prior history of psychotic disorders were not excluded from any of these studies. No deaths were associated with psychotic disorders; the incidents that did occur were managed by study drug or trial participation discontinuation, with subsequent resolution of the events.

Among the double-blind-placebo controlled studies, the number of psychosis AEs was too low to allow a meaningful conclusion. Only 5 subjects experienced a total of 6 AEs of psychotic disorder. Of these AEs, 3 (0.6%) occurred in 2 subjects receiving placebo and 3 (0.3%) in 3 subjects receiving perampanel. Two of these AEs were considered as mild in severity, 3 moderate and 1 severe. Of the 6 AEs of psychotic disorders, 4 were defined as serious and resulted in discontinuation of treatment or study; 2 SAEs occurred in a subject receiving placebo (5136-4013, Study 304), and 2 in 2 subjects receiving perampanel (1105-5006, Study 305; 2757-6001, Study 306). The time to first occurrence of AEs of psychotic disorder was included in the submission.

Given the lower incidence of AEs of psychotic disorders in the perampanel groups compared to the placebo in the double-blind Phase III studies, no contraindication and/or warning in the PI are considered necessary by the sponsor.

Risk of abuse

There are insufficient data to support potential risk of abuse and dependency on perampanel for patients with a history of drug abuse, therefore, Eisai believes that this information does not need to be added to the product information.

The development program of perampanel has incorporated a detailed assessment of abuse liability in nonclinical and in clinical studies, as well as in postmarketing pharmacovigilance activities. The overall nonclinical and clinical data for perampanel do not support more restrictive scheduling than the last 3 approved AEDs namely lacosamide, pregabalin, and retigabine.

Risks of dependency and abuse/misuse are already identified as potential risks in the risk management plan (RMP), and are AE's of interest for assessment in the EU Post Approval Safety Study (PASS) 402. The objective of the study is to address the need for additional safety information on AEs of interest in the categories of important identified risks, important potential risks, and important missing information.

Perampanel will only be available by prescription to a population of patients diagnosed with epilepsy. Patients with epilepsy are not expected to be at particularly high risk for recreational abuse of the drug and this is expected to limit the availability of perampanel to inappropriate populations of diverters and abusers.

The potential for adverse drug-drug interactions is low. There is a potential for pharmacodynamic interactions between perampanel and other drugs causing sedative effects (such as sedatives, hypnotics, and alcohol). Caution should be exercised when using alcohol and/or these medications with perampanel, and this is stated in the proposed perampanel labelling.

Overall, it is unlikely that perampanel is associated with a major risk to public health related to its abuse. Perampanel, the starting material, intermediates and major metabolites are not viable chemical precursors to any known controlled substance. The recent EMA Pharmacovigilance Risk Assessment Committee (PRAC) report of 6 February 2014 (covering the PSUR Period 23 January 2013 to 22 July 2013) concluded that "*that there is insufficient evidence for an association between Fycompa use and drug abuse, dependency and withdrawal.*" All data taken together indicate that the overall profile of perampanel is comparable to other approved AEDs, including pregabalin, retigabine, and lacosamide.

In summary, considering the overall profile of perampanel in polydrug users in Studies 023 and 024, which included dose dependent negative effects and unwillingness to try the drug again, it is highly unlikely that perampanel would have abuse liability in current and previous drug abusers.

4. *The benefit/risk balance for perampanel in patients aged 65 years appears to be unfavourable. The committee is requested to provide advice on the use of perampanel in this population.*

Perampanel has been approved in over 36 countries, including US, Europe, Canada and Switzerland. In every country the indication has included patients 65 years old and above.

Clinical studies of perampanel in epilepsy did not include sufficient numbers of patients aged 65 years and greater to determine whether they respond differently than did younger patients. Perampanel safety information in the elderly can be gathered from perampanel studies conducted in other indications (Parkinson's disease, neuropathic pain) that included a large elderly patient population (total number of elderly subjects exposed to perampanel = 905 and total number of elderly subjects exposed to placebo = 450). The data indicated that in elderly subjects perampanel doses up to 8 mg showed comparable incidence of TEAEs of dizziness, fatigue, irritability and fall, for which elderly are at higher risk, to those observed in the age group of < 65 years.

In the epilepsy Phase III double-blind studies falls occurred slightly more frequently in the perampanel treated subjects than the placebo treated subjects regardless of age. This relationship is most apparent in the elderly subjects but Eisai's opinion is that this could be a chance finding due to the small size of the group.

Of the 73 falls that occurred in the total perampanel group during double-blind treatment, 44 (60.3%) occurred in association with seizures, that is,, either occurred on the same day as a seizure or were noted as seizure associated by the investigator.

Eisai acknowledges that falls and dizziness occurred slightly more frequently in the perampanel treated subjects than the placebo treated subjects regardless of age. Fall in the whole population (particularly in the elderly) is described in the updated RMP as an important identified risk and is included in the *Precautions* section of the PI.

> *"There appears to be an increased risk of falls, particularly in the elderly; the underlying reason is unclear"*

Additionally, in a population pharmacokinetic analysis of subjects with partial onset seizures ranging in age from 12 to 74 years, no significant effect of age on perampanel clearance was found. Thus, elderly subjects show no differences in perampanel exposure compared to younger subjects.

Overall, Eisai believes that the data support a conclusion that no age limit exclusion from the indication is necessary and proposes instead that

"Perampanel should be used with caution in the elderly".

Other issues raised by delegate

Aggression: The Delegate requested clarity on the difference between the incidence of psychiatric events reported in the proposed Australian Label compared to the USPI.

The incidence of aggression stated in the Australia Product Information was based on the Medical Dictionary for Regulatory Activities (MedDRA), Preferred Term (PT) of the treatment-emergent adverse events (TEAEs) reported in the Double-Blind Phase III POS Trials. In the USPI, the TEAEs from the same Double-Blind Phase III POS pooled database were evaluated using standard MedDRA queries (SMQs) for *hostility- and aggression related events*, and grouped into Narrow SMQ and Narrow & Broad SMQ, per request by FDA.

- Narrow SMQ identifies cases likely to represent the condition of interest, for example anger, physical assault [Table 19]
- Broad SMQ identifies all possible cases, including some that may be of little or no interest on closer inspection, for example skin laceration
- A narrow and broad search includes both "narrow" scope terms and the additional "broad" scope terms [Table 20]

Table 19. TEAEs (Relevant Narrow SMQ Terms for hostility/aggression) by decreasing frequency: Double-blind Phase III POS trails

TEAE Category	Placebo[b]	Perampanel[b]				
MedDRA Preferred Term[a]	(N=442) n (%)	2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Any TEAE	3 (0.7)	1 (0.6)	2 (1.2)	12 (2.8)	16 (6.3)	31 (3.0)
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17(1.6)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.7)	12 (1.2)
Belligerence	0	0	0	0	1 (0.4)	1 (0.1)
Physical assault	0	0	1 (0.6)	0	0	1 (0.1)

Table 20. TEAEs (Relevant Narrow and Broad SMQ Terms for hostility/aggression) in ≥2 patients in any group by decreasing frequency: Double-blind Phase III POS trails

TEAE Category	Placebo[b]	Perampanel[b]				
MedDRA Preferred Term[a]	(N=442) n (%)	2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Any TEAE	25 (5.7)	9 (5.0)	9 (5.2)	53 (12.3)	52 (20.4)	123 (11.8)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)	73 (7.0)
Aggression	2 (0.5)	1 (0.6)	1 (0.6)	7 (1.6)	8 (3.1)	17 (1.6)
Skin laceration	7 (1.6)	1 (0.6)	0	7 (1.6)	6 (2.4)	14 (1.3)
Anger	1 (0.2)	0	0	5 (1.2)	7 (2.7)	12 (1.2)
Agitation	2 (0.5)	0	0	3 (0.7)	1 (0.4)	4 (0.4)
Abnormal behavior	0	0	0	2 (0.5)	2 (0.8)	4 (0.4)
Laceration	0	0	0	2 (0.5)	1 (0.4)	3 (0.3)
Affect lability	0	0	0	0	2 (0.8)	2 (0.2)

TEAEs (Relevant Narrow SMQ Terms for Hostility/Aggression) from Double-Blind Phase III POS Trials have been summarized in Table 19, while TEAEs (Relevant Narrow & Broad SMQ Terms for Hostility/Aggression) in ≥2 Patients in Any Group from Double-Blind Phase 3 POS Trials summarized in Table 20.

Based on Table 20, the Fycompa US Prescription Information (PI), under the heading of Warnings and Precautions, states *"In the controlled Phase 3 epilepsy clinical trials, hostility- and aggression- related adverse reactions occurred in 12% and 20% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group."*

Risk management plan negotiation/agreement

Though not included as part of the Delegate overview queries, Eisai has taken the opportunity to respond further to the Delegates clarification of the labelling concerns related to Risk Management. In addition the sponsor provided an updated Australian Specific Annex (ASA) to the RMP which highlights specific Risk Management activities to be undertaken for Australia. The sponsor's commitment to meet the RMP and Delegate's concerns were outlined in the response but is beyond the scope of this AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Fycompa film coated tablets containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg of perampanel (as hemisesquihydrate) to have an overall positive benefit–risk profile for the indication;

> *The adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM advised that the amendments to the Product Information (PI) and Consumer Medicine Information (CMI) should be limited to the following:

- Statements in the *Dosage and Administration* section regarding dose escalation and dose titration
- A statement in the *Precautions* section of the PI and the relevant sections of the CMI that perampanel should be used with caution in patients 65 years and older.
- A statement in the *Precautions* section of the PI that perampanel be used with caution in patients with psychosis as well as more information regarding dose titration in this circumstance.
- Amendment of the CMI to better reflect Australian circumstances and with reference to the standard CMI template and the Usability Guidelines.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the committee consider initial prescribing should be limited to neurologists?*

The ACPM noted that treatment with perampanel would most likely be intitiated by neurologists and that other medicines available on the Australian market for epilepsy restrict prescribing to neurologists, which did not seem to be overburdensome for patients and doctors. However, as the benefit-risk profile of perampanel was of less concern than some of the medicines which are required to be prescribed by neurologists, the ACPM advised that initial prescribing need not be limited to neurologists.

2. *Does the committee consider the 12 mg dose should be restricted to patients taking concomitant strong CYP3A4 inducers?*

The ACPM considered that it was not necessary to restrict use of the 12 mg dose to patients taking strong CYP3A4 inducers as other patients may also benefit from a dose increase to 12 mg. However, the ACPM considered that 8 mg should be trialled and if necessary increased with caution to 12 mg depending on patient tolerance and that this should be reflected in the PI.

3. *Should the PI contain a statement to the effect that perampanel is not recommended in patients with a history of psychosis, low impulse control or drug abuse?*

The ACPM was of the view that perampanel may be useful in some patients with pyschosis or with a history of drug abuse where other agents have failed and that use of the medicine should not be precluded. The ACPM noted that the psychiatric side effects of perampanel were similar to other antiepileptic medicines currently available in Australia. However, the ACPM considered that the PI should highlight that perampanel should be used with extreme caution in patients with psychosis and include more information regarding dose titration in this circumstance.

4. *The benefit-risk balance for perampanel in patients aged ≥65 years appears to be unfavourable. The committee is requested to provide advice on the use of perampanel in this population group.*

The ACPM agreed with the sponsor's argument in the pre ACPM response that the data support no age limit exclusion from the indication and therefore perampanel should not be restricted to patients less than 65 years of age. However, the ACPM advised that the PI and the CMI should warn prescribers that perampanel should be used with caution in the elderly with reference to the risks.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Fycompa (perampanel hemisesquihydrate 2, 4, 6, 8, 10 and 12 mg) film-coated tablet blister for oral administration for the following indication;

> *Fycompa is indicated for the adjunctive treatment of partial-onset seizures with or Without secondary generalised seizures patients with epilepsy aged12 years and older.*

Specific conditions of registration applying to these goods

The implementation of EU-RMP Version 1.5 (dated 22/05/2012, DLP 01/12/2010 and Australian Specific Annex (dated May 2014), and any future updates (where TGA approved) for Perampanel (Fycompa).

Attachment 1. Product Information

The Product Information approved for main Fycompa the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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