"To be sold by retail on the prescription Neurologist only"

TORPANEL

Warning: serious psychiatric and behavioral reactions.

- **Serious or life-threate ning psychiatric and behavioural adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking perampanel tablet.**
- **Monitor patients for these reactions as well as for changes in mood, behaviour, or personality that are not typical for the patient, particularly during the titration period and at higher doses**
- **Perampanel tablet should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

1. **Generic Name**
   Perampanel Tablets
2. **Qualitative and quantitative composition**

TORPANEL 2

Each film coated tablet Contains
Perampanel……..2mg
Colours: Yellow oxide of Iron, Red oxide of Iron and Titanium Dioxide I.P.

The excipients used are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F530067 orange (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Yellow oxide of Iron, Red oxide of Iron).

TORPANEL 4

Each film coated tablet Contains:
Perampanel……..4mg
Colours: Red oxide of Iron and Titanium Dioxide I.P.

The excipients used are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F565145 Brown (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Red oxide of Iron).

TORPANEL 6

Each film coated tablet Contains
Perampanel…….6 mg
Colours: Red oxide of Iron, Titanium Dioxide I.P

The excipients used are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F540192 Pink (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Red oxide of Iron).

TORPANEL 8

Each film coated tablet Contains:
Perampanel……...8 mg
Colours: Red oxide of Iron, Black Oxide of Iron, Titanium Dioxide I.P.

The excipients used are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F500030 Purple (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Red oxide of Iron, Black oxide of Iron).

TORPANEL 10

Each film coated tablet contains:
Perampanel……10 mg
Colours: Yellow oxide of Iron, Indigo carmine aluminium lake & Titanium Dioxide I.P.
The excipients used are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F510060 Green (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Indigo carmine aluminium lake, Yellow oxide of Iron).

TORPANEL 12

Each film coated tablet contains:
Perampanel……..12 mg
Colours: Indigo carmine aluminium lake & Titanium Dioxide I.P.
The excipients used are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F505080 Blue (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Indigo carmine aluminium lake).

3. Dosage form and strength

Dosage Form: Film coated Tablets

Strength: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg

4. Clinical particulars

4.1 Therapeutic indication

For the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

For the adjunctive treatment of primary generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older.

4.2 Posology and method of administration

Posology

Adults and adolescents

Perampanel must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.

Perampanel should be taken orally once daily at bedtime.

Partial-Onset Seizures

Reportedly, Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective

therapy in partial-onset seizures.

Treatment with Perampanel 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 (either weekly or every 2 weeks as per half-life considerations described below) 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 medicinal products that do not shorten the half-life of perampanel (see section *Drug Interactions*) should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section *Drug Interactions*) should be titrated no more frequently than at 1-week intervals.

*Withdrawal*It is recommended that discontinuation be undertaken gradually to minimise the potential for rebound seizures. However, due to its long half-life and subsequent slow decline in plasma concentrations, perampanel can be discontinued abruptly if absolutely needed.

Missed doses

Single missed dose: As perampanel has a long half-life, the patient should wait and take their next dose as scheduled.

If more than 1 dose has been missed, for a continuous period of less than 5 half-lives (3 weeks for patients not taking perampanel metabolism-inducing anti-epileptic drugs (AED), 1 week for patients taking perampanel metabolism-inducing AEDs (see section *Drug Interactions*), consideration should be given to re-start treatment from the last dose level.

If a patient has discontinued perampanel for a continuous period of more than 5 half- lives, it is recommended that initial dosing recommendations given above should be followed.

Elderly (65 years of age and above)

Reported clinical studies of Perampanel in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Analysis of reported safety information in 905 perampanel-treated elderly subjects (in double-blind studies conducted in non-epilepsy indications) revealed no age- related differences in the safety profile. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose-adjustment in the elderly is not required. Perampanel should be used with caution in elderly taking into account the drug interaction potential in polymedicated patients (see section *Special warnings and precautions for use*).

Renal impairment

Dose adjustment is not required in patients with mild renal impairment. Use in patients with moderate or severe renal impairment or patients undergoing haemodialysis is not recommended.

Hepatic impairment

Dose increases in patients with mild and moderate hepatic impairment should be based on clinical response and tolerability. For patients with mild or moderate hepatic impairment, dosing can be initiated at 2 mg. Patients should be up-titrated using 2 mg doses no faster than every 2 weeks based on tolerability and effectiveness.

Perampanel dosing for patients with mild and moderate impairment should not exceed 8 mg. Use in patients with severe hepatic impairment is not recommended.

Paediatric population

The safety and efficacy of perampanel in children below 12 years of age have not been established yet. No data are available.

Method of administration

Perampanel should be taken as single oral dose at bedtime. It may be taken with or without food (see section *Pharmacokinetic properties*). The tablet should be swallowed

Whole with a glass of water. It should not be chewed, crushed or split. The tablets cannot be split accurately as there is no break line.

4.3 Contraindications

Hypersensitivity to active substances or to any of the excipients of this product.

4.4 Special warnings and precautions for use

WARNING

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Warning: serious psychiatric and behavioral reactions.

- **Serious or life-threate ning psychiatric and behavioural adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking perampanel tablet.**
- **Monitor patients for these reactions as well as for changes in mood, behaviour, or personality that are not typical for the patient, particularly during the titration period and at higher doses**
- **Perampanel tablet should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products in several indications. A meta-analysis of reported randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for perampanel.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported (frequency unknown; see section *Undesirable effects*) in association with perampanel treatment.

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. Symptoms of DRESS include typically, although not exclusively, fever, rash associated with other organ system involvement, lymphadenopathy, liver function tests abnormalities and eosinophilia. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If signs and symptoms suggestive of these reactions appear, perampanel should be withdrawn immediately and an alternative treatment considered (as appropriate).

Nervous system disorders

Perampanel may cause dizziness and somnolence and therefore may influence the ability to drive or use machines (see section *Effects on ability to drive and use machines*).

Oral contraceptives

At doses of 12 mg/day Perampanel may decrease the effectiveness of progestative-containing hormonal contraceptives; in this circumstance additional non-hormonal forms of contraception are recommended when using Perampanel (see section *Drugs interactions*).

Falls

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

Aggression

Aggressive and hostile behaviour has been reported in patients receiving perampanel therapy. As per reported data, in perampanel-treated patients in clinical trials, aggression, anger and irritability were reported more frequently at higher doses. Most of the reported events were either mild or moderate and patients recovered either spontaneously or with dose adjustment. However, thoughts of harming others, physical assault or threatening behaviour were observed in some patients (<1% in perampanel clinical studies). Patients and caregivers should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted. The dosage of perampanel should be reduced if such symptoms occur and should be discontinued immediately if symptoms are severe.

Abuse potential

Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of perampanel abuse.

Concomitant CYP3A inducing anti-epileptic medicinal products

Response rates after addition of perampanel at fixed doses were less when patients received concomitant CYP3A enzyme-inducing anti-epileptic medicinal products (carbamazepine, phenytoin, oxcarbazepine) as compared to response rates in patient who received concomitant non-enzyme-inducing anti-epileptic medicinal products. Patients' response should be monitored when they are switching from concomitant non- inducer anti-epileptic medicinal products to enzyme inducing medicinal products and vice versa. Depending upon individual clinical response and tolerability, the dose may be increased or decreased 2 mg at a time (see section *Posology and method of administration*).

Other concomitant (non- anti-epileptic) cytochrome P450 inducing or inhibiting medicinal products

Patients should be closely monitored for tolerability and clinical response when adding or

removing cytochrome P450 inducers or inhibitors, since perampanel plasma levels can be decreased or increased; the dose of perampanel may need to be adjusted accordingly.

4.5 Drugs interactions

Perampanel is not considered a strong inducer or inhibitor of cytochrome P450 or UGT enzymes (see section *Pharmacokinetic properties*).

Oral contraceptives

As per reported data, in healthy women receiving 12 mg (but not 4 or 8 mg/day) for 21 days concomitantly with a combined oral contraceptive, Perampanel was shown to decrease the levonorgestrel exposure (mean C_{max} and AUC values were each decreased by 40%). Ethinylestradiol AUC was not affected by Perampanel 12 mg whereas C_{max} was decreased by 18%. Therefore, the possibility of decreased efficacy of progestative-containing oral contraceptives should be considered for women needing Perampanel 12 mg/day and an additional reliable method (intra-uterine device (IUD), condom) is to be used (see section *Special warnings and precautions for use*).

Interactions between Perampanel and other anti-epileptic medicinal products

Potential interactions between Perampanel (up to 12 mg once daily) and other anti- epileptic drugs (AEDs) were assessed in reported clinical studies and evaluated in the population PK analysis of four pooled Phase 3 studies including patients with partial- onset seizures and primary generalised tonic-clonic seizures. The effect of these interactions on average steady state concentration is summarised in the following table.

AED coadministered	**Influence of AED on Perampanel concentration**	**Influence of Perampanel on AED concentration**
Carbamazepine	2.75 fold decrease	<10% decrease
Clobazam	No influence	<10% decrease
Clonazepam	No influence	No influence
Lamotrigine	No influence	<10% decrease
Levetiracetam	No influence	No influence
Oxcarbazepine	1.9 fold decrease	35% increase [1)]
Phenobarbital	No influence	No influence
Phenytoin	1.7 fold decrease	No influence
Topiramate	19% decrease	No influence
Valproic Acid	No influence	<10% decrease
Zonisamide	No influence	No influence

1) Active metabolite monohydroxycarbazepine was not assessed.

Some anti-epileptic drugs known as CYP450 3A enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) have been shown to increase perampanel clearance and consequently to decrease plasma concentrations of perampanel. Conversely, withdrawal of a concomitant CYP450 3A enzyme inducer can be expected to increase plasma concentrations of perampanel and dose reduction may be required.

Carbamazepine, a known potent enzyme inducer, reduced perampanel levels by two- thirds in a study performed on healthy subjects.

A similar result was seen in a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in placebo- controlled clinical trials. The total clearance of Perampanel was increased when administered with carbamazepine (2.75-fold), phenytoin (1.7-fold) and oxcarbazepine (1.9-fold), which are known inducers of enzymes of metabolism (see section *Pharmacokinetic properties*). This effect should be taken into account and managed when adding or withdrawing these anti-epileptic drugs from a patient's treatment regimen.

In a population pharmacokinetic analysis of patients with partial-onset seizures receiving Perampanel up to 12 mg/day in reported placebo-controlled clinical trials, Perampanel did not affect to a clinically relevant manner the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, zonisamide, carbamazepine, clobazam, lamotrigine and valproic acid, at the highest perampanel dose evaluated (12 mg/day).

In the reported epilepsy population pharmacokinetic analysis, perampanel was found to decrease the clearance of oxcarbazepine by 26%. Oxcarbazepine is rapidly metabolised by cytosolic reductase enzyme to the active metabolite, monohydroxycarbazepine. The effect of perampanel on monohydroxycarbazepine concentrations is not known.

Perampanel is dosed to clinical effect regardless of other AEDs.

Effect of perampanel on CYP3A substrates

In healthy subjects, Perampanel (6 mg once daily for 20 days) decreased midazolam AUC by 13%. A larger decrease in exposure of midazolam (or other sensitive CYP3A substrates) at higher Perampanel doses cannot be excluded.

Effect of cytochrome P450 inducers on perampanel pharmacokinetics

Strong inducers of cytochrome P450, such as rifampicin and hypericum, are expected to decrease perampanel concentrations and the potential for higher plasma concentrations of reactive metabolites in their presence has not been excluded. Felbamate has been shown to decrease the concentrations of some medicinal products and may also reduce perampanel concentrations.

Effect of cytochrome P450 inhibitors on perampanel pharmacokinetics

As per reported data, in healthy subjects, the CYP3A4 inhibitor ketoconazole (400 mg once daily for 10 days) increased perampanel AUC by 20% and prolonged perampanel half-life by 15% (67.8 h vs 58.4 h). Larger effects cannot be excluded when perampanel is combined with a CYP3A inhibitor with longer half-life than ketoconazole or when the inhibitor is given for a longer treatment duration.

Levodopa

In healthy subjects, Perampanel (4 mg once daily for 19 days) had no effect on C_{max} or AUC of levodopa.

Alcohol

The effects of perampanel on tasks involving alertness and vigilance such as driving ability were additive or supra-additive to the effects of alcohol itself, as found in a reported pharmacodynamic interaction study in healthy subjects. Multiple dosing of perampanel 12 mg/day increased levels of anger, confusion, and depression as assessed using the Profile of Mood State 5-point rating scale (see section *Pharmacodynamic properties*). These effects may also be seen when Perampanel is used in combination with other central nervous system (CNS) depressants.

Paediatric population

Interaction studies have only been performed in adults.

In a population pharmacokinetic analysis of the adolescent patients in the reported Phase 3 clinical studies, there were no notable differences between this population and the overall population.

4.6 Use in special populations (such as pregnant women, lactating women, paediatricpatients, geriatric patients etc.)

Women of childbearing potential and contraception in males and females

Perampanel is not recommended in women of childbearing potential not using contraception unless clearly necessary.

Pregnancy

There are limited amounts of data (less than 300 pregnancy outcomes) from the use of perampanel in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats at maternally toxic doses (see section *Preclinical safety data*). Perampanel is not recommended during pregnancy.

Breast-feeding

Studies in lactating rats have shown excretion of perampanel and/or its metabolites in milk (for details see section *Preclinical safety data*). It is not known whether perampanel is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Perampanel therapy taking into account the benefit of breast--feeding for the child and the benefit of therapy for the woman.

Fertility

In the fertility study in rats, prolonged and irregular oestrous cycles were observed at high-dose (30 mg/kg) in females; however, these changes did not affect the fertility and early embryonic development. There were no effects on male fertility (see section *Preclinical safety data*). The effect of perampanel on human fertility has not been established.

4.7 Effects on ability to drive and use machines

Perampanel has moderate influence on the ability to drive and use machines.

Perampanel may cause dizziness and somnolence and, therefore, may influence the ability to drive or use machines. Patients are advised not to drive a vehicle, operate complex machinery or engage in other potentially hazardous activities until it is known whether perampanel affects their ability to perform these tasks (see sections *Special warnings and precautions for use* and *Drugs interactions*).

4.8 Undesirable effects

Summary of the safety profile

In all reported controlled and uncontrolled trials in patients with partial-onset seizures, 1,639 subjects have received perampanel of whom 1,147 have been treated for 6 months and 703 for longer than 12 months.

In the reported controlled and uncontrolled trial in patients with primary generalised tonic-clonic seizures, 114 subjects have received perampanel of whom 68 have been treated for 6 months and 36 for longer than 12 months.

Adverse reactions leading to discontinuation:

In the reported controlled Phase 3 partial-onset seizures clinical trials, the rate of discontinuation as a result of an adverse reaction was 1.7%, 4.2% and 13.7% in patients randomised to receive perampanel at the recommended doses of 4 mg, 8 mg and 12 mg/day, respectively, and 1.4% in patients randomised to receive placebo. The adverse reactions most commonly (≥ 1% in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence.

In the reported controlled Phase 3 primary generalised tonic-clonic seizures clinical trial, the rate of discontinuation as a result of an adverse reaction was 4.9% in patients randomised to receive perampanel 8 mg, and 1.2% in patients randomised to receive placebo. The adverse reaction most commonly leading to discontinuation (≥ 2% in the perampanel group and greater than placebo) was dizziness.

Post-marketing use

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with perampanel treatment (see section *Special warnings and precautions for use*).

Tabulated list of adverse reactions

In the table below, adverse reactions, which were identified based on review of the full Perampanel clinical studies safety database, are listed by System Organ Class and frequency. The following convention has been used for the classification of adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), not known (cannot be estimated from the available data).

Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Very common	Common	Uncommon	Not known
Metabolism and nutrition disorders		Decreased appetite Increased appetite		

Psychiatric disorders		Aggression Anger Anxiety Confusional state	Suicidal ideation Suicide attempt	
Nervous system disorders	Dizziness	Ataxia		
	Somnolence	Dysarthria Balance disorder Irritability		
Eye disorders		Diplopia Vision blurred		
Ear and labyrinth disorders		Vertigo		
Gastrointestinal disorders		Nausea		
Skin and subcutaneous tissue disorders				Drug Reaction with Eosinophilia and Systemic Symptoms
Musculoskeletal and connective tissue disorders		Back pain		
General disorders		Gait disturbance Fatigue		
Investigations		Weight increased		

Injury, poisoning and procedural complications		Fall		

* See section *Special warnings and precautions for use*

Paediatric population

Based on the clinical trial database of 196 adolescents exposed to perampanel from reported double-blind studies for partial-onset seizures and primary generalised tonic-clonic seizures, the overall safety profile in adolescents was similar to that of adults, except for aggression, which was observed more frequently in adolescents than in adults.

- **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

There is limited clinical experience with perampanel overdose in humans. In a report of an intentional overdose that could have resulted in a dose up to 264 mg, the patient experienced events of altered mental status, agitation and aggressive behaviour and recovered without sequelae. There is no available specific antidote to the effects of perampanel. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. In view of its long half- life, the effects caused by perampanel could be prolonged. Because of low renal clearance special interventions such as forced diuresis, dialysis or haemoperfusion are unlikely to be of value.

5 Pharmacological properties

5.1 Mechanism of Action

Perampanel is a first-in-class 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 overexcitation. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. In in vitro studies, perampanel did not compete with AMPA for binding to the AMPA receptor, but perampanel binding was displaced by noncompetitive AMPA receptor antagonists, indicating that perampanel is a noncompetitive AMPA receptor antagonist. In vitro, perampanel inhibited AMPA-induced (but not NMDA-induced) increase in intracellular calcium. In vivo, perampanel significantly prolonged seizure latency in an AMPA-induced seizure model.

The precise mechanism by which perampanel exerts its antiepileptic effects in humans remains to be fully elucidated.

5.2 Pharmacodynamic properties

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 reported efficacy trials for partial-onset seizures. In addition, a pharmacokinetic-pharmacodynamic (efficacy) analysis was performed in one reported efficacy trial for primary generalised tonic-clonic seizures. In both analyses, perampanel

exposure is correlated with reduction in seizure frequency.

Psychomotor performance

Single and multiple doses of 8 mg and 12 mg impaired psychomotor performance in healthy volunteers in a dose-related manner. The effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Psychomotor performance testing returned to baseline within 2 weeks of cessation of perampanel dosing.

Cognitive function

In a reported healthy volunteer study to assess the effects of perampanel on alertness, and memory using a standard battery of assessments, no effects of perampanel were found following single and multiple doses of perampanel up to 12 mg/day.

In a reported placebo controlled study conducted in adolescent patients, no significant changes in cognition relative to placebo as measured by Cognitive Drug Research (CDR) System Global Cognition Score were observed for perampanel. In the open label extension, no significant changes were observed in global CDR system score after 52 weeks of perampanel treatment (see section *Pharmacodynamic properties-Paediatric population*).

Alertness and mood

Levels of alertness (arousal) decreased in a dose-related manner in healthy subjects dosed with perampanel from 4 to 12 mg/day. Mood deteriorated following dosing of 12 mg/day only; the changes in mood were small and reflected a general lowering of alertness. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion and depression as assessed using the Profile of Mood State 5-point rating scale.

Cardiac electrophysiology

Perampanel did not prolong the QTc interval when administered in daily doses up to 12 mg/day, and did not have a dose-related or clinically important effect on QRS duration.

Clinical efficacy and safety

Partial-Onset Seizures

The efficacy of perampanel in partial-onset seizures was established in three reported adjunctive therapy 19 week, randomised, double-blind, placebo-controlled, multicentre trials in adult and adolescent patients. Subjects had partial-onset seizures with or without secondary generalisation and were not adequately controlled with one to three concomitant AEDs. During a 6-week baseline period, subjects were required to have more than five seizures with no seizure-free period exceeding 25 days. In these three trials, subjects had a mean duration of epilepsy of approximately 21.06 years. Between 85.3% and 89.1% of patients were taking two to three concomitant AEDs with or without concurrent vagal nerve stimulation.

Two studies (studies 304 and 305) compared doses of perampanel 8 and 12 mg/day with placebo and the third study (study 306) compared doses of perampanel 2, 4 and 8 mg/day with placebo. In all three trials, following a 6-week Baseline Phase to establish baseline seizure frequency prior to randomisation, subjects were randomised and titrated to the randomised dose. During the Titration Phase in all three trials, treatment was initiated at 2 mg/day and increased in weekly increments of 2 mg/day to the target dose. Subjects experiencing intolerable adverse events could remain on the same dose or have their dose

decreased to the previously tolerated dose. In all three trials, the Titration Phase was followed by a Maintenance Phase that lasted 13 weeks, during which patients were to remain on a stable dose of perampanel.

The pooled 50% responder rates were placebo 19%, 4 mg 29%, 8 mg 35% and 12 mg 35%. A statistically significant effect on the reduction in 28-day seizure frequency (Baseline to Treatment Phase) as compared to the placebo group was observed with perampanel treatment at doses of 4 mg/day (Study 306), 8 mg/day (Studies 304, 305 and 306), and 12 mg/day (Studies 304 and 305). The 50% responder rates in the 4 mg, 8 mg and 12 mg groups were respectively 23.0%, 31.5%, and 30.0% in combination with enzyme-inducing anti-epileptic medicinal products and were 33.3%, 46.5% and 50.0% when perampanel was given in combination with non-enzyme-inducing anti-epileptic medicinal products. These studies show that once-daily administration of perampanel at doses of 4 mg to 12 mg was significantly more efficacious than placebo as adjunctive treatment in this population.

Data from placebo-controlled studies demonstrate that improvement in seizure control is observed with a once-daily perampanel dose of 4 mg and this benefit is enhanced as the dose is increased to 8 mg/day. No efficacy benefit was observed at the dose of 12 mg as compared to the dose of 8 mg in the overall population. Benefit at the dose of 12 mg was observed in some patients who tolerate the dose of 8 mg and when the clinical response to that dose was insufficient. A clinically meaningful reduction in seizure frequency relative to placebo was achieved as early as the second week of dosing when patients reached a daily dose of 4 mg.

1.7 to 5.8% of the patients on perampanel in the clinical studies became seizure free during the 3 month maintenance period compared with 0%-1.0% on placebo

Open label extension study

Ninety-seven percent of the patients who completed the randomised trials in patients with partial-onset seizures were enrolled in the open label extension study (n = 1186). Patients from the randomised trial were converted to perampanel over 16 weeks followed by a long term maintenance period (≥ 1 year). The mean average daily dose was 10.05 mg.

Primary Generalised Tonic-Clonic Seizures

Perampanel as adjunctive therapy in patients 12 years of age and older with idiopathic generalised epilepsy experiencing primary generalised tonic-clonic seizures was established in a reported multicenter, randomised, double-blind, placebo-controlled study (Study 332). Eligible patients on a stable dose of 1 to 3 AEDs experiencing at least 3 primary generalised tonic-clonic seizures during the 8-week baseline period were randomised to either perampanel or placebo. The population included 164 patients (perampanel N = 82, placebo N = 82). Patients were titrated over four weeks to a target dose of 8 mg per day or the highest tolerated dose and treated for an additional 13 weeks on the last dose level achieved at the end of the titration period. The total treatment period was 17 weeks. Study drug was given once per day.

The 50% primary generalised tonic-clonic seizures responder rate during the Maintenance Period was significantly higher in the perampanel group (58.0%) than in the placebo group (35.8%), P = 0.0059. The 50% responder rate was 22.2% in combination with enzyme-inducing anti-epileptic medicinal products and was 69.4% when perampanel was given in combination with non-enzyme-inducing anti-epileptic medicinal products. The number of perampanel subjects taking enzyme-inducing anti- epileptic medicinal products was small (n = 9). The median percent change in primary generalised tonic-clonic seizure frequency

per 28 days during the Titration and Maintenance Periods (combined) relative to Prerandomisation was greater with perampanel (-76.5%) than with placebo (-38.4%), P < 0.0001. During the 3 months maintenance period, 30.9% (25/81) of the patients on perampanel in the clinical studies became free of PGTC seizures compared with 12.3% (10/81) on placebo.

Other subtypes of idiopathic generalised seizure

The efficacy and safety of perampanel in patients with myoclonic seizures have not been established. The available data are insufficient to reach any conclusions.

The efficacy of perampanel in the treatment of absence seizures has not been demonstrated.

In Study 332, in patients with PGTC seizures who also had concomitant myoclonic seizures, freedom from seizures was achieved in 16.7% (4/24) on perampanel compared to 13.0% (3/23) in those on placebo. In patients with concomitant absence seizures, freedom from seizures was achieved in 22.2% (6/27) on perampanel compared to 12.1% (4/33) on placebo. Freedom from all seizures was achieved in 23.5% (19/81) of patients on perampanel compared to 4.9% (4/81) of patients on placebo.

Open label extension phase

Of the 140 subjects who completed the Study 332, 114 subjects (81.4%) had entered the Extension phase. Patients from the randomised trial were converted to perampanel over 6 weeks followed by a long term maintenance period (≥ 1 year). In the Extension Phase, 73.7% of subjects have a modal daily perampanel dose of greater than 4 to 8 mg/day and 16.7% had a modal daily dose of greater than 8 to 12 mg/day. A decrease in PGTC seizure frequency of at least 50% was seen in 65.9% of subjects after 1 year of treatment during the Extension Phase (relative to their pre-perampanel baseline seizure frequency). These data were consistent with those for percent change in seizure frequency and showed that the PGTC 50% responder rate was generally stable across time from about week 26 through the end of year 2. Similar results were seen when all seizures and absence vs. myoclonic seizures were evaluated over time.

Conversion to monotherapy

In a reported retrospective study of clinical practice, 51 patients with epilepsy who received perampanel as adjunctive treatment converted to perampanel monotherapy. The majority of these patients had a history of partial onset seizures. Of these, 14 patients (27%) reverted to adjunctive therapy in the following months. Thirty four (34) patients were followed up for at least 6 months and, of these, 24 patients (71%) remained on perampanel monotherapy for at least 6 months. Ten (10) patients were followed up for at least 18 months and, of these, 3 patients (30%) remained on perampanel monotherapy for at least 18 months.

Paediatric population

The three reported pivotal double-blind placebo-controlled phase 3 studies included 143 adolescents between the ages of 12 and 18. The results in these adolescents were similar to those seen in the adult population.

Study 332 included 22 adolescents between the ages of 12 and 18. The results in these adolescents were similar to those seen in the adult population.

A reported 19-week, randomised, double-blind, placebo-controlled study with an open-label extension phase (Study 235) was performed to assess the short-term effects on cognition of Perampanel (target dose range of 8 to 12 mg once daily) as adjunctive therapy

in 133 (Perampanel n = 85, placebo n = 48) adolescent patients, ages 12 to less than 18 years old, with inadequately controlled partial-onset seizures. Cognitive function was assessed by the Cognitive Drug Research (CDR) System Global Cognition t-Score, which is a composite score derived from 5 domains testing Power of Attention, Continuity of Attention, Quality of Episodic Secondary Memory, Quality of Working Memory, and Speed of Memory. The mean change (SD) from baseline to end of double- blind treatment (19 weeks) in CDR System Global Cognition t-Score was 1.1 (7.14) in the placebo group and (minus) –1.0 (8.86) in the perampanel group, with the difference between the treatment groups in LS means (95% CI) = (minus) -2.2 (-5.2, 0.8). There was no statistically significant difference between the treatment groups (p = 0.145). CDR System Global Cognition t-Scores for placebo and perampanel were 41.2 (10.7) and 40.8 (13.0), respectively at the baseline. For patients with perampanel in the open label extension (n = 112), the mean change (SD) from baseline to end of open-label treatment (52 weeks) in CDR System Global Cognition t-Score was (minus) -1.0 (9.91). This was not statistically significant (p = 0.96). After up to 52 weeks of treatment with perampanel (n = 114), no effect on bone growth was observed. No effects on weight, height and sexual development were seen following up to 104 weeks of treatment (n = 114).

5.3. Pharmacokinetic properties

As per reported data, the pharmacokinetics of perampanel have been studied in healthy adult subjects (age range 18 to 79), adults and adolescents with partial-onset seizures and primary generalised tonic-clonic seizures, adults with Parkinson's disease, adults with diabetic neuropathy, adults with multiple sclerosis, and subjects with hepatic impairment.

Absorption

Perampanel is readily absorbed after oral administration with no evidence of marked first-pass metabolism. Co-administration of perampanel tablets with a high fat meal had no impact on the peak plasma exposure (C_{max}) or total exposure ($AUC_{0\text{-}inf}$) of perampanel. The t_{max} was delayed by approximately 1 hour compared to that under fasted conditions.

Distribution

Data from reported *in vitro* studies indicate that perampanel is approximately 95% bound to plasma proteins.

In vitro studies show that perampanel is not a substrate or significant inhibitor of organic anion transporting polypeptides (OATP) 1B1 and 1B3, organic anion transporters (OAT) 1, 2, 3, and 4, organic cation transporters (OCT) 1, 2, and 3, and the efflux transporters P-glycoprotein and Breast Cancer Resistance Protein (BCRP).

Biotransformation

Perampanel is extensively metabolised via primary oxidation and sequential glucuronidation. The metabolism of perampanel is mediated primarily by CYP3A based on reported clinical study results in healthy subjects administered radiolabeled perampanel and supported by reported *in vitro* studies using recombinant human CYPs and human liver microsomes.

Following administration of radiolabeled perampanel, only trace amounts of perampanel metabolites were observed in plasma.

Elimination

Following administration of a radiolabeled perampanel dose to either 8 healthy adults or elderly subjects, approximately 30% of recovered radioactivity was found in the urine and

70% in the faeces. In urine and faeces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. In a population pharmacokinetic analysis of pooled data from 19 reported Phase 1 studies, the average $t_{½}$ of perampanel was 105 hours. When dosed in combination with the strong CYP3A inducer carbamazepine, the average $t_{½}$was 25 hours.

Linearity/non-linearity

In healthy subjects, plasma concentrations of perampanel increased in direct proportion to administered doses over the range of 2 to 12 mg. In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in placebo-controlled clinical trials, a linear relationship was found between dose and perampanel plasma concentrations.

Special populations

Hepatic impairment

The pharmacokinetics of perampanel following a single 1 mg dose were evaluated in 12 subjects with mild and moderate hepatic impairment (Child-Pugh A and B, respectively) compared with 12 healthy, demographically matched subjects. The mean apparent clearance of unbound perampanel in mildly impaired subjects was 188 ml/min vs. 338 ml/min in matched controls, and in moderately impaired subjects was 120 ml/min vs. 392 ml/min in matched controls. The $t_{½}$ was longer in mildly impaired (306 h vs. 125 h) and moderately impaired (295 h vs. 139 h) subjects compared to matched healthy subjects.

Renal impairment

The pharmacokinetics of perampanel have not been formally evaluated in patients with renal impairment. Perampanel is eliminated almost exclusively by metabolism followed by rapid excretion of metabolites; only trace amounts of perampanel metabolites are observed in plasma. In a population pharmacokinetic analysis of patients with partial-onset seizures having creatinine clearances ranging from 39 to 160 mL/min and receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel clearance was not influenced by creatinine clearance. In a population pharmacokinetic analysis of patients with primary generalised tonic-clonic seizures receiving perampanel up to 8 mg/day in a placebo-controlled clinical study, perampanel clearance was not influenced by baseline creatinine clearance.

Gender

In a population pharmacokinetic analysis of patients with partial-onset seizures receiving perampanel up to 12 mg/day and patients with primary generalised tonic- clonic seizures receiving perampanel up to 8 mg/day in reported placebo-controlled clinical trials, perampanel clearance in females (0.54 l/h) was 18% lower than in males (0.66 l/h).

Elderly (65 years of age and above)

In a population pharmacokinetic analysis of patients with partial-onset seizures (age range 12 to 74 years) and primary generalised tonic-clonic seizures (age range 12 to 58 years), and receiving perampanel up to 8 or 12 mg/day in placebo-controlled clinical trials, no significant effect of age on perampanel clearance was found. A dose adjustment in the elderly is not considered to be necessary (see section *Posology and method of administration*).

Paediatric population

In a reported population pharmacokinetic analysis of the adolescent patients pooled from the Phase 2 and 3 clinical studies, there were no notable differences between this population and the overall population.

Drug interaction studies

In vitro assessment of drug interactions

Drug metabolising enzyme inhibition

In human liver microsomes, perampanel (30 µmol/l) had a weak inhibitory effect on CYP2C8 and UGT1A9 among major hepatic CYPs and UGTs.

Drug metabolising enzyme induction

Compared with positive controls (including phenobarbital, rifampicin), perampanel was found to weakly induce CYP2B6 (30 µmol/l) and CYP3A4/5 (≥ 3 µmol/l) among major hepatic CYPs and UGTs in cultured human hepatocytes.

6 Nonclinical properties

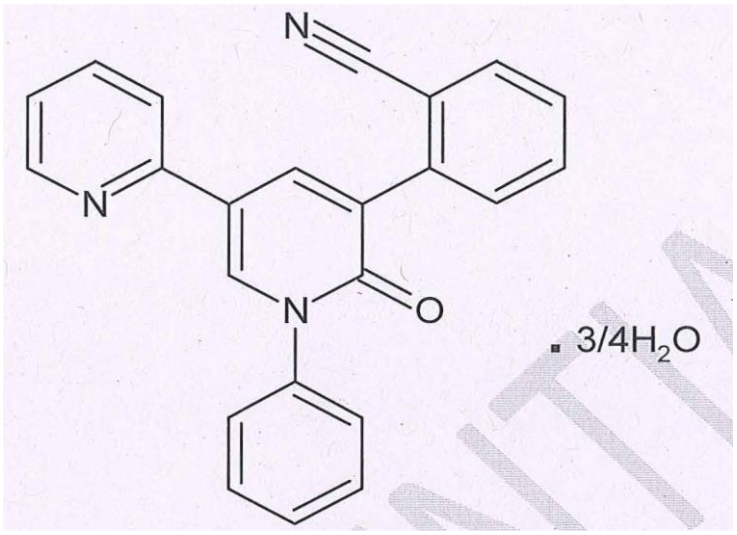
6.1 Animal Toxicology or Pharmacology

Adverse reactions not observed in reported clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In the reported fertility study in rats, prolonged and irregular oestrous cycles were observed at the maximum tolerated dose (30 mg/kg) in females; however, these changes did not affect fertility and early embryonic development. There were no effects on male fertility. The excretion into breast milk was measured in rats at 10 days post-partum. Levels peaked at one hour and were 3.65 times the levels in plasma. In a reported pre- and postnatal development toxicity study in rats, abnormal delivery and nursing conditions were observed at maternally toxic doses, and the number of stillbirths was increased in offspring. Behavioural and reproductive development of the offspring was not affected, but some parameters of physical development showed some delay, which is probably secondary to the pharmacology-based CNS effects of perampanel. The placental transfer was relatively low; 0.09% or less of administered dose was detected in the foetus. Nonclinical data reveal that perampanel was not genotoxic and had no carcinogenic potential. The administration of maximum tolerated doses to rats and monkeys resulted in pharmacologically-based CNS clinical signs and decreased terminal body weight. There were no changes directly attributable to perampanel in clinical pathology or histopathology.

7 Description

Chemical name of Perampanel is (2-Cyanophenyl)-5-(2-pyridyl)-1-phertyl-1,2-dihydropyridin-2-one hydrate. Molecular formula is C_{23}H1sN3/4 H2O and Molecular weight is 362.90. Chemical structure is:



TORPANEL 2
Orange colored, round, biconvex, film-coated tablet debossed '2' on one side and plain on other side.

TORPANEL 4
Red colored, round, biconvex, film-coated tablet debossed '4' on one side and plain on other side.

TORPANEL 6

Pink colored, round, biconvex, film-coated tablet debossed '6' on one side and plain on other side.

TORPANEL 8

Light Brown colored, round, biconvex, film coated tablet debossed "8" on one side and plain on other side.

TORPANEL 10

Green colored, round, biconvex, film coated tablet debossed "10" on one side and plain on other side.

TORPANEL 12

Blue colored, round, biconvex, film coated tablet debossed "12" on one side and plain on other side.

8 Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Available in blister pack of 10 Tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from light and moisture. Keep out of reach of children.

9 Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible

What is in this leaflet?

1. What **TORPANEL** is and what it is used for
2. What you need to know before you use **TORPANEL**
3. How to use **TORPANEL**
4. Possible side effects
5. How to store **TORPANEL**
6. Contents of the pack and other information

9.1 What TORPANEL is and what it is used for

TORPANEL contains a medicine called perampanel. It belongs to a group of medicines called anti epileptics. These medicines are used to treat epilepsy - where someone has repeated fits (seizures). It has been given to you by your doctor to reduce the number of fits that you have.

TORPANEL is used: For the adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

For the adjunctive treatment of primary generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older

9.2 What you need to know before you use

TORPANEL Do not use TORPANEL if:

- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking perampanel.
- If you are allergic to perampanel or any of the other ingredients of this medicine.

Warnings and precautions

Warning: serious psychiatric and behavioral reactions.

- **Serious or life-t h reate ning psychiatric and behavioural adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking perampanel tablet.**
- **Monitor patients for these reactions as well as for changes in mood, behaviour, or personality that are not typical for the patient, particularly during the titration period and at higher doses**
- **Perampanel tablet should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

Talk to your doctor before taking **TORPANEL** if you have liver problems or moderate or severe kidney problems

You should not take **TORPANEL** if you have serious liver problems or moderate or serious kidney problems.

Before taking this medicine you should tell your doctor if you have a history of alcoholism or drug dependence.

- **TORPANEL** may make you feel dizzy or sleepy, particularly at the beginning of treatment.
- **TORPANEL** may make you more likely to fall over, particularly if you are an older person; this might be due to your illness.
- **TORPANEL** may make you aggressive, angry or violent. It may also cause you to have unusual or extreme changes in behaviour or mood.

Talk to your doctor if any of the above applies to you.

A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor straight away.

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of **TORPANEL**.

- DRESS typically, although not exclusively, appears as flu-like symptoms and a rash with a high body temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

If you experience any of the above after taking **TORPANEL** (or you are not sure) talk to your doctor or pharmacist.

Children
TORPANEL is not recommended for children aged under 12. The safety and effectiveness are not yet known in this age group.

Other medicines and TORPANEL
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because TORPANEL **can** affect the way some other medicines Work. Also some medicines can affect the way **TORPANEL** works. Do not start or stop other medicines without talking to your doctor or pharmacist.

- Other anti-epileptic medicines, such as carbamazepine, oxcarbazepine, and phenytoin that are used to treat fits may affect **TORPANEL**. Tell your doctor if you are taking or have recently taken these medicines as your dose may need to be adjusted.
- Felbamate (a medicine used to treat epilepsy) may also affect **TORPANEL**. Tell your doctor if you are taking or have recently taken this medicine as your dose may need to be adjusted.
- Midazolam (a medicine used to stop prolonged, acute (sudden) convulsive seizures, for sedation and sleep problem) may be affected by **TORPANEL**. Tell your doctor if you are taking midazolam as your dose may need to be adjusted.
- Some other medicines such as rifampicin (a medicine used to treat bacterial infections), hypericum (St. John's Wort) (a medicine used to treat mild anxiety) and ketoconazole (a medicine used to treat fungal infections) may affect **TORPANEL**.

Tell your doctor if you are taking or have recently taken these medicines as your dose may need to be adjusted.

- Oral contraceptives (also called "hormonal contraceptives").

Tell your doctor if you are taking hormonal contraceptives. TORPANEL may make certain hormonal contraceptives such as levonorgestrel less effective. You should use other forms of safe and effective contraception (such as a condom or coil) when taking TORPANEL. You should continue doing this for one month after stopping treatment. Discuss with your doctor what may be appropriate contraception for you.

TORPANEL with alcohol

Speak to your doctor before drinking alcohol. Be careful about consuming alcohol with epilepsy medicines including **TORPANEL**.

- Drinking alcohol while taking **TORPANEL** can make you less alert and affect your ability to drive or use tools or machines.

- Drinking alcohol while taking **TORPANEL** can also make any feelings of anger, confusion or sadness worse.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. Do not stop treatment without first discussing it with your doctor.

- **TORPANEL** is not recommended in pregnancy.

- You must use a reliable method of contraception to avoid becoming pregnant while you are being treated with **TORPANEL**. You should continue doing this for one month after stopping treatment. Tell your doctor if you are taking hormonal contraceptives. **TORPANEL** may make certain hormonal contraceptives such as levonorgestrel less effective. You should use other forms of safe and effective contraception (such as a condom or coil) when taking **TORPANEL**. You should also do this for one month after stopping treatment. Discuss with your doctor what may be appropriate contraception for you.

It is not known whether the ingredients of **TORPANEL** can pass into breast milk.

The doctor will weigh up the benefit and risks to your baby of taking **TORPANEL** While you are breast-feeding.

Driving and using machines

Do not drive or use machines until you know how **TORPANEL** affects you.

You must talk to your doctor about the effect of your epilepsy on driving and using machines.

- **TORPANEL** may make you feel dizzy or sleepy, particularly at the beginning of treatment. If this happens to you, do not drive or use any tools or machines.
- Drinking alcohol while taking **TORPANEL** may make these effects worse.

9.1 How to use TORPANEL

Always take **TORPANEL** exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much to take

The usual starting dose is 2 mg once a day before you go to bed.

- Your doctor may increase this in 2 mg steps to a maintenance dose between 4 mg

and 12 mg - depending on your response.

- If you have mild or moderate liver problems, your dose should not be more than 8 mg each day and your dose increases should be at least 2 weeks apart.
- Don't take more **TORPANEL** than your doctor has recommended. It may take a few weeks to find the right dose of **TORPANEL** for you.

How to take
Swallow the tablet whole with a glass of water. You can take **TORPANEL** with or without food. Do not chew, crush or split the tablet. The tablets cannot be split accurately as there is no break line.

If you take more TORPANEL than you should
If you have taken more **TORPANEL** than you should contact your doctor straight away. You may experience confusion, agitation and aggressive behaviour.

If you forget to take TORPANEL
- If you forget to take a tablet, wait until your next dose and then carry on as usual.
- Do not take a double dose to make up for a forgotten dose.
- If you have missed less than 7 days of treatment with **TORPANEL**, continue taking your daily tablet as originally instructed by your doctor.
- If you have missed more than 7 days of treatment with **TORPANEL**, talk to your doctor immediately.

If you stop taking TORPANEL
Take **TORPANEL** for as long as your doctor recommends. Do not stop unless your doctor advises you to. Your doctor may reduce your dose slowly to avoid your fits (seizures) coming back or getting worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.2 Possible Side Effects

Like all medicines, these tablets can cause side effects, although not everybody gets them. A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor straight away.

Very common (may affect more than 1 user in 10) are:

- feeling dizzy
- feeling sleepy (drowsiness or somnolence)

Common (may affect more than 1 user in 100) are:

- increased or decreased appetite, weight gain
- feeling aggressive, angry, irritable, anxious or confused
- difficulty with walking or other balance problems (ataxia, gait disturbance, balance disorder)
- slow speech (dysarthria)
- blurred vision or double vision (diplopia)
- spinning sensation (vertigo)

- feeling sick (nausea)
- back pain
- feeling very tired (fatigue)
- falling down

Uncommon (may affect more than 1 user in 1000) are:

- thoughts about harming yourself or ending your own life (suicidal thoughts), tried to end your
- own life (attempted suicide)

Not known (the frequency of this side effect cannot be estimated from the available data) are:

- widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome).

Stop using **TORPANEL** if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 9.2.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.3 How to store TORPANEL

Keep out of the sight and reach of children.

Store at a temperature not exceeding 30°C, protected from light and moisture.

Do not use **TORPANEL** after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.4 Contents of the pack and other information

What TORPANEL contains:

TORPANEL 2

The active substance in this product is Perampanel.

The other ingredients are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F530067 orange (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Yellow oxide of Iron, Red oxide of Iron).

TORPANEL 4

The active substance in this product is Perampanel.

The other ingredients are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F565145 Brown (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Red oxide of Iron).

TORPANEL 6

The active substance in this product is Perampanel.

The other ingredients are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F540192 Pink (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Red oxide of Iron).

TORPANEL 8

The active substance in this product is Perampanel.

The other ingredients are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F500030 Purple (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Red oxide of Iron, Black oxide of Iron).

TORPANEL 10

The active substance in this product is Perampanel.

The other ingredients are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F510060 Green (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Indigo carmine aluminium lake, Yellow oxide of Iron).

TORPANEL 12

The active substance in this product is Perampanel.

The other ingredients are Micro crystalline cellulose, Low substituted Hydroxy propyl cellulose, Lactose, Iso propyl Alcohol, Magnesium Stearate, Povidone, Opadry 03F505080 Blue (contains Hypromellose, Talc, PEG 8000, Titanium Dioxide, Indigo carmine aluminium lake).

10 Details of manufacturer

Manufactured by:
Torrent Pharmaceuticals LTD
VIll. Bhud & Makhnu Majra,
Teh. Baddi – 173 205, Dist. Solan (H.P.), INDIA

11 Details of permission or licence number with date

MNB/05/183 dated 19.11.2020

12 Date of revision

MAR-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TORPANEL 2, 4, 6, 8, 10 and 12/MAR-2022/03/PI