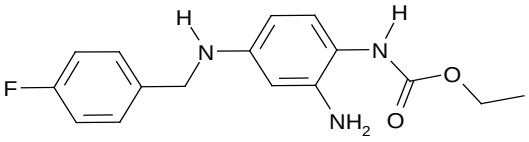
TROBALT®

PRODUCT INFORMATION

NAME OF THE MEDICINE Retigabine

Structure:



Chemical Name: N-[2-Amino-4-(4-fluorophenyl-methylamino)-phenyl]carbamic acid ethyl ester

Molecular Formula: C16H18FN3O2

CAS Number: 150812-12-7

DESCRIPTION

Retigabine is a white to pinkish-brown solid with a molecular weight of 303.3. It is practically insoluble in water, soluble in methanol and chloroform and freely soluble dimethylformamide.

Trobalt film-coated tablets also contain the inactive ingredients croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose. The film coat includes polyvinyl alcohol, titanium dioxide, purified talc, indigo carmine aluminium lake, cochineal, iron oxide yellow, lecithin and xanthum gum.

The excipient lecithin is derived from soy.

PHARMACOLOGY

Pharmacodynamics:

Mechanism of action

Potassium channels are one of the voltage-gated ion channels found in neuronal cells and are important determinants of neuronal activity. *In vitro* studies indicate that retigabine acts primarily through opening neuronal potassium channels (KCNQ2 [Kv7.2] and KCNQ3 [Kv7.3]). This stabilises the resting membrane potential and controls the sub-threshold electrical excitability in neurons, thus preventing the initiation of epileptiform action potential bursts. Mutations in the KCNQ channels underlie several human inheritable disorders, including epilepsy (KCNQ2 and 3). A further contribution to the activity of retigabine may be through augmentation of GABA-mediated currents. The mechanism of action of retigabine on potassium channels has been well documented, however other mechanisms by which retigabine may assert an antiepileptic effect have yet to be fully elucidated.

In a range of seizure models, retigabine increased the threshold for seizure induction produced by maximal electroshock, pentylenetetrazol, picrotoxin and N-methyl-D-aspartate. Retigabine also displayed inhibitory properties in multiple kindling

models, both during kindling development and in the fully kindled state. In addition, retigabine was effective in preventing status epilepticus seizures in rodents with cobalt-induced epileptogenic lesions, and inhibiting tonic extensor seizures in genetically susceptible mice. The relevance of these models to human epilepsy, however, is not known.

Pharmacodynamic effects

In rats, retigabine increased the sleep time induced by sodium thiopentone from approximately 4 minutes to 53 minutes, and the propofol-induced sleep time from approximately 8 minutes to 12 minutes. There was no effect on sleep time induced by halothane or sodium methohexitone. Retigabine may increase the duration of anaesthesia induced by some anaesthetics (e.g. thiopentone).

Pharmacokinetics:

Absorption

After both single and multiple oral doses, retigabine is rapidly absorbed with median T_{max} values generally between 0.5 and 2 hours. Absolute oral bioavailability of retigabine relative to an intravenous dose is approximately 60%.

Although administration of retigabine with a high fat meal resulted in a delay in T_{max} (by approximately 45 minutes) and an increase in C_{max} (by 38%), there was no change in the overall extent of retigabine absorption. Therefore retigabine may be taken with or without food.

Distribution

Retigabine is approximately 80% bound to plasma protein over the concentration range of 0.1 to 2 µg/mL. The steady state volume of distribution of retigabine is 2 to 3 L/kg following intravenous dosing.

Metabolism

Retigabine is extensively metabolised in humans. A substantial fraction of the retigabine dose is converted to inactive N-glucuronides. Retigabine is also metabolised to an N-acetyl metabolite (NAMR) that is also subsequently glucuronidated. NAMR has antiepileptic activity, but is less potent than retigabine in animal seizure models.

There is no evidence for hepatic oxidative metabolism of retigabine or NAMR by cytochrome P450 enzymes. Therefore co-administration with inhibitors or inducers of cytochrome P450 enzymes is unlikely to affect the pharmacokinetics of retigabine or NAMR (see Interactions with Other Medicines).

Excretion

Excretion is predominantly by the renal route. A total of approximately 84% of the dose is recovered in the urine, including NAMR (18%), N-glucuronides of the parent drug and of NAMR (24%), or parent drug (36%). Only 14% of retigabine is excreted in the faeces. Retigabine has a plasma half-life of approximately 6 to 10 hours. The total clearance of retigabine from plasma following intravenous dosing is typically 0.4 to 0.6 L/h/kg.

Linearity

Retigabine pharmacokinetics are essentially linear over the single dose range of 25 to 600 mg in healthy volunteers and up to 1200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Special Populations:

Renal Impairment

In a single dose study, the retigabine AUC was increased by approximately 30% in volunteers with mild renal impairment (creatinine clearance 50 to 80 mL/min) and by approximately 100% in volunteers with moderate to severe renal impairment (creatinine clearance <50 mL/min), relative to healthy volunteers. The effect of mild renal impairment on retigabine AUC is not considered clinically significant, therefore no adjustment of the retigabine dose is recommended. However, adjustment of the retigabine dose is recommended in patients with moderate to severe renal impairment (see Dosage and Administration).

In a single dose study in healthy volunteers and subjects with end stage renal disease, the retigabine AUC was increased by approximately 100% in the subjects with end stage renal disease, relative to healthy volunteers. However, the effect of haemodialysis on retigabine clearance was not adequately evaluated.

Hepatic Impairment

In a single dose study, there were no clinically significant effects on retigabine AUC in volunteers with mild hepatic impairment (Child-Pugh score 5 to 6). The retigabine AUC was increased by approximately 50% in volunteers with moderate hepatic impairment (Child-Pugh score 7 to 9) and by approximately 100% in volunteers with severe hepatic impairment (Child-Pugh score >9), relative to healthy volunteers. Adjustment of the retigabine dose is recommended in patients with moderate or severe hepatic impairment (see Dosage and Administration).

Children

The pharmacokinetics of retigabine in children and adolescents have not been investigated.

Elderly

In a single-dose study, retigabine was eliminated more slowly by healthy elderly volunteers (66 to 82 years of age) relative to healthy young adult volunteers, resulting in a higher AUC (approximately 40 to 50%) and longer terminal half-life (30%) (see Dosage and Administration).

Other patient characteristics

Data from clinical studies show there were no clinically meaningful effects of gender, race or body weight on the pharmacokinetics of retigabine. No dosage adjustment is necessary on the basis of these characteristics.

CLINICAL TRIALS

Clinical efficacy of adjunctive retigabine therapy in partial onset seizures

Three multicentre, randomized, double-blind, placebo-controlled studies (Studies 301, 302 and 205) in a total of 1239 adult patients have been conducted to assess the efficacy of TROBALT as adjunctive therapy of partial onset seizures, with or without secondary generalisation. All patients enrolled were to have had seizures that were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs), and more than 75% of all patients were taking ³ 2 concurrent AEDs. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to12 per 28 days. Patients were randomised to placebo or TROBALT at 600, 900, or 1200 mg/day (see Table 1). During an 8-week baseline period, patients had to experience ³ 4 partial onset seizures per 28 days. Patients could not be seizure-free for ³ 21 days. The total duration of the titration and maintenance phases was 16 or 18 weeks.

The primary efficacy endpoints were:

- percentage change in the 28-day total partial seizure frequency from baseline to the double-blind phase (titration and maintenance phases combined)

- responder rate (defined as the percentage of patients with a ³ 50% reduction in 28-day total partial seizure frequency) from baseline to the maintenance phase (Studies 301 and 302 only).

TROBALT was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies (Table 1). TROBALT was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1200 mg/day (two studies).

Table 1 Summary of percentage changes in 28-day total partial seizure frequency and responder rates

Study (n=population in double-blind phase; n=population in maintenance phase)	**Placebo**	**TROBALT**		
		600 mg/day	**900 mg/day**	**1200 mg/day**
Study 205 (n=396; n=303)				
Total partial seizure frequency (median) % change	-13%	-23%	-29%*	-35%*
Responder rate	26%	28%	41%	41%*
Study 301 (n=305; n=256)				
Total partial seizure frequency (median) % change	-18%	~	~	-44%*
Responder rate	23%	~	~	56%*
Study 302 (n=538; n=471)				
Total partial seizure frequency (median) % change	-16%	-28%*	-40%*	~
Responder rate	19%	39%*	47%*	~

* Statistically significant, p≤0.05
~ Dose not studied

In open-label extensions of the three placebo-controlled studies, persistence of efficacy was maintained over an evaluation period of at least 12 months.

INDICATIONS

Adjunctive treatment of drug resistant partial onset seizures with or without secondary generalisation, in patients with epilepsy where other appropriate drug combinations have proved inadequate or have not been tolerated.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Patients requiring renal dialysis

PRECAUTIONS

Eye disorders

Pigment changes (discolouration) of ocular tissues, including the retina have been reported in long-term clinical studies with TROBALT. These occurred in approximately a third of the patients who developed skin discolouration but retinal pigment changes have also occurred in patients who did not have skin discolouration. Scleral and conjunctival discoloration, on the white of the eye and inside eyelids has also been observed.

Pigment changes in the retina have the potential to cause serious eye disease with loss of vision. It is not yet known whether the retinal pigment changes caused by

TROBALT lead to visual impairment, although several patients have been reported to have impaired visual acuity.

A comprehensive ophthalmological examination (including visual acuity, slit-lamp examination, and dilated fundoscopy) should be performed in all patients at baseline and at least every six month thereafter while treatment is ongoing. If any abnormality is detected, TROBALT should be discontinued unless no other treatment options are available. If continued, the patient should be monitored more closely and the prescriber and the patient should discuss the potential risks assessed against the benefits of maintained treatment with TROBALT.

Skin Discolouration

Skin discolouration has been reported in patients taking TROBALT in long term clinical trials, however not all patients have been examined and the incidence may increase with increasing duration of exposure. The blue skin discoloration is seen predominantly on or around the lips or in the nail beds of the fingers and toes, but more widespread involvement of the face and legs has also occurred. The skin discoloration generally occurred after 4 years of treatment with TROBALT but has appeared sooner in some patients. If a patient develops skin discoloration, serious consideration should be given to changing to an alternate medication.

Urinary retention

As a potassium channel opener, TROBALT can reduce the contractility of urinary bladder smooth muscle which can cause urinary retention.

In the placebo-controlled epilepsy trials, “urinary retention,” “urinary hesitation,” and “dysuria” were reported in 0.9%, 2.2%, and 2.3% of patients on TROBALT, respectively, and in 0.5%, 0.9%, and 0.7% of patients on placebo, respectively.

Because of the increased risk of urinary retention on TROBALT, urologic symptoms should be carefully monitored. Closer monitoring is recommended for patients who have other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients), or patients who use concomitant medications that may affect voiding (e.g., anticholinergics). In these patients, a comprehensive evaluation of urologic symptoms prior to and during treatment with TROBALT may be appropriate.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that TROBALT titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTc) of up to 6.7 ms (upper bound of 95% one-sided CI 12.6 ms) was observed within 3 hours of dosing. Caution should be taken when TROBALT is prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment with TROBALT and in those with a corrected QT interval >440ms at baseline, an ECG should be recorded on reaching the maintenance dose.

Psychiatric disorders

Confusional state, psychotic symptoms, and hallucinations were reported more frequently as adverse reactions in patients treated with TROBALT than in those treated with placebo in placebo-controlled epilepsy trials. Discontinuations resulting from these reactions were more common in the drug-treated group. These effects were dose-related and generally appeared within the first 8 weeks of treatment. Half of the patients in the controlled trials who discontinued TROBALT due to hallucinations or psychosis required hospitalization. Approximately two-thirds of patients with psychosis in controlled trials had no prior psychiatric history. The psychiatric symptoms in the vast majority of patients in both controlled and open label trials resolved within 7 days of discontinuation of TROBALT. Rapid titration at greater than the recommended doses appeared to increase the risk of psychosis and hallucinations.

Suicidal behaviour and ideation

Anti-epileptic drugs increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analysis of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. The table below shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Table of risk by indication for anti-epileptic drugs in pooled analysis

Indication	Placebo patients with events/ 1000 patients	Drug patients with events/ 1000 patients	Relative Risk: Incidence of events in Drug patients/incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing TROBALT or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Withdrawal seizures

As with other AEDs, TROBALT must be withdrawn gradually to minimise the potential for rebound seizures. It is recommended that the TROBALT dose is reduced over a period of at least 3 weeks, unless safety concerns require an abrupt withdrawal.

Ability to perform tasks that require judgement, motor or cognitive skills

Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see Adverse Effects). It is recommended that patients are advised about the risk of such adverse reactions at treatment initiation and following each titration step, and that they are advised not to drive or operate machinery until they have established how TROBALT affects them.

As there is individual variation in response to all AED therapy, it is recommended that prescribers discuss with patients the specific issues of epilepsy and driving.

Effects on Fertility:

The effect of retigabine on human fertility has not been established.

There were no treatment-related effects of retigabine on fertility in animal studies. However, the plasma levels achieved in these studies were less than those reached at therapeutic doses.

Use in Pregnancy (Category B3):

There are no adequate and well-controlled studies of TROBALT in pregnant women.

Retigabine and/or its metabolites have been shown to cross the placenta in rats, resulting in tissue concentrations that were similar in mothers and fetuses.

Oral administration of retigabine to pregnant animals was associated with maternal plasma exposures to retigabine and its major circulating metabolite, NAMR, below those reached at therapeutic doses. No teratogenic effects were observed in these studies, but oral administration of retigabine throughout pregnancy and lactation at maternally toxic doses resulted in increased pre- and postnatal mortality, decreased body weight gain and delayed reflex development in the offspring.

Use in Lactation:

It is not known if retigabine is excreted in human milk. However, retigabine and/or its metabolites were present in the milk of lactating rats. In a developmental study in this species, administration of retigabine throughout pregnancy and lactation at maternally toxic doses resulted in increased pre- and postnatal mortality, decreased body weight gain and delayed reflex development in the offspring. Maternal plasma exposures to retigabine and NAMR were likely to be less than those in humans at the MRHD. There are insufficient data available to make a recommendation concerning breast feeding, but it should be noted that juvenile rats showed increased sensitivity to retigabine compared with their more mature counterparts.

Paediatric Use:

The safety and efficacy of TROBALT has not been established in patients below 18 years of age. In juvenile animal studies, increased sensitivity to acute neurotoxicity and urinary bladder toxicity was observed in young rats compared to adults. In studies in which rats were dosed from postnatal day 7, retigabine-related mortality, clinical signs of neurotoxicity, and renal and urinary tract toxicities were observed at oral doses of 2 mg/kg/day or greater. The no-effect level was associated with retigabine exposures (plasma AUC) less than those in human adults at the MRHD of 1,200 mg per day. In studies in which dosing began on postnatal day 28, acute central nervous system effects, but no apparent renal or urinary tract effects, were observed at oral doses of 30 mg/kg/day, associated with plasma retigabine exposures less than those achieved clinically at the MRHD. TROBALT is not recommended for use in patients below 18 years of age.

Use in the Elderly:

Only 8 patients aged over 65 years were enrolled in clinical trials to assess efficacy and safety of TROBALT in partial epilepsy. Patients aged over 65 years may be at increased risk of central nervous system events, urinary retention and atrial fibrillation. TROBALT must be used with caution in this population and a reduced initial and maintenance dose is recommended.

Genotoxicity:

Retigabine was not mutagenic in either bacterial or mammalian cells, and the major circulating metabolite NAMR was not mutagenic in a bacterial assay. Retigabine and NAMR were clastogenic in *in vitro* chromosomal aberration assays. Retigabine was, however, negative in an *in vivo* mouse micronucleus assay and rat *in vivo* /*in vitro* UDS assay. On the weight of evidence, retigabine is not considered a genotoxic hazard to humans.

Carcinogenicity:

In a one-year neonatal mouse carcinogenicity assay, a small dose-related increase in the frequency of lung neoplasms (bronchoalveolar carcinoma and combined adenoma/carcinoma) was observed in treated males. The clinical significance of this is uncertain. Retigabine was not carcinogenic in a 2-year carcinogenicity assay in rats. The plasma levels achieved in these studies were considerably less than those reached in humans at the MRHD.

Effect on laboratory tests:

Retigabine has been shown to interfere with clinical laboratory assays of both serum and urine bilirubin, which can result in falsely elevated readings.

INTERACTIONS WITH OTHER MEDICINES

There is no evidence for hepatic oxidative metabolism of retigabine or NAMR by cytochrome P450 enzymes. Therefore co-administration with inhibitors or inducers of cytochrome P450 enzymes is unlikely to affect the pharmacokinetics of retigabine or NAMR (see Interactions with Other Medicines).

In vitro studies using human liver microsomes showed little or no potential for retigabine to inhibit the major cytochrome P450 isoenzymes (including CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5). In addition, retigabine and NAMR did not induce CYP1A2 or CYP3A4/5 in human primary hepatocytes. Therefore retigabine is unlikely to affect the pharmacokinetics of substrates of the major cytochrome P450 isoenzymes through inhibition or induction mechanisms.

Other antiepileptic drugs

Based on an analysis of pooled data from clinical studies, retigabine did not cause clinically significant effects on the plasma trough concentrations of the following AEDs:

- Carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, pregabalin, topiramate, valproate, zonisamide.

Based on an analysis of pooled data from clinical studies, there were no clinically significant effects of the following AEDs on retigabine pharmacokinetics:

- Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, topiramate, valproate.

Interaction with digoxin

Data from an *in vitro* study showed that the N-acetyl metabolite of retigabine (NAMR) inhibited P-glycoprotein-mediated transport of digoxin in a concentration-dependent manner, indicating that NAMR may inhibit renal clearance of digoxin. Administration of retigabine at therapeutic doses may increase digoxin serum concentrations.

Interaction with phenytoin

Steady-state data from a limited number of patients in smaller phase II studies indicated that phenytoin can reduce retigabine systemic exposure by 35%. If adding phenytoin to TROBALT consider increasing the dose of TROBALT

Interaction with carbamazepine

Steady-state data from a limited number of patients in smaller phase II studies indicated that carbamazepine can reduce retigabine systemic exposure by 33%. If adding carbamazepine to retigabine consider increasing the dose of TROBALT.

Interaction with alcohol

Co-administration of ethanol (1.0 g/kg) with retigabine (200 mg) resulted in an increase in visual blurring in healthy volunteers. It is recommended that patients are advised about the possible effects on vision if they take retigabine with alcohol.

Oral contraceptives

At retigabine doses of up to 750 mg/day, there was no clinically significant effect of retigabine on the pharmacokinetics of the estrogen (ethinyl estradiol) or progestogen (norgestrel, norethindrone) components of the oral contraceptive pill. Furthermore, given the lack of in-vitro activity of retigabine on human cytochrome P450s (see Pharmacokinetic section - Metabolism), no interactions are anticipated for retigabine doses greater than 750 mg/day. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine.

ADVERSE EFFECTS

Table 3 below lists adverse events incidence in placebo-controlled adjunctive trials in adult patients with partial onset seizures (adverse events in at least 2% of patients treated with TROBALT in any treatment group and numerically more frequent than in the placebo group.)

Table 3 Adverse events occuring in at least 2% of patients treated with TROBALT in any treatment group and numerically more frequent than in the placebo group.

Body System/ Adverse Event	Placebo (N = 427) %	TROBALT 600 mg/day (N = 281) %	TROBALT 900 mg/day (N = 273) %	TROBALT 1,200 mg/day (N = 259) %	TROBALT All (N = 813) %
Eye					
Diplopia	2	8	6	7	7
Blurred vision	2	2	4	10	5
Gastrointestinal					
Nausea	5	6	6	9	7
Constipation	1	1	4	5	3
Dyspepsia	2	3	2	3	2
General					
Fatigue	6	16	15	13	15
Asthenia	2	4	6	4	5
Infections and infestations					
Influenza	2	4	1	5	3
Investigations					
Weight increased	1	2	3	3	3
Nervous system					
Dizziness	9	15	23	32	23
Somnolence	12	15	25	27	22
Memory impairment	3	3	6	9	6
Tremor	3	3	10	12	8
Vertigo	2	8	8	9	8
Abnormal coordination	3	5	5	12	7
Disturbance in attention	<1	6	6	7	6
Gait disturbance	1	2	5	6	4
Aphasia	<1	1	3	7	4
Dysarthria	<1	4	2	8	4
Balance disorder	<1	3	3	5	4
Paraesthesia	2	3	2	5	3
Amnesia	<1	<1	3	3	2
Dysphasia	<1	1	1	3	2
Psychiatric					
Confusional state	3	4	8	16	9
Anxiety	2	3	2	5	3
Disorientation	<1	<1	<1	5	2
Psychotic disorder	0	0	<1	2	<1
Renal and urinary					
Dysuria	<1	1	2	4	2
Urinary hesitation	<1	2	1	4	2
Haematuria	<1	2	1	2	2
Chromaturia	<1	<1	2	3	2

In clinical trials TROBALT was associated with a weight gain of 2.2kg by week 18. There was a clear dose trend, with the highest dose group showing a mean gain of 2.7kg. Approximately 17% of individuals given TROBALT experienced weight gain of ≥ 7% from baseline by week 18, with the highest risk at 1200mg/d (19.1%).

Table 4 Major Neuro-Psychiatric Symptoms in Placebo-Controlled Epilepsy Trials

Adverse Reaction	Number (%) With Adverse Reaction		Number (%) Discontinuing	
	TROBALT(n = 813)	Placebo (n = 427)	TROBALT (n = 813)	Placebo (n = 427)
Confusional state	75 (9%)	11 (3%)	32 (4%)	4 (<1%)
Psychosis	9 (1%)	0	6 (<1%)	0
Hallucinations[a]	14 (2%)	2 (<1%)	6 (<1%)	0

[a] Hallucinations includes visual, auditory, and mixed hallucinations

Clinical trial data

Overall, the most frequently reported adverse reactions in patients receiving TROBALT (≥4% and occurring approximately twice the placebo rate) were dizziness (23%), somnolence (22%), fatigue (15%), confusional state (9%), vertigo (8%), tremor (8%), abnormal coordination (7%), diplopia (7%), disturbance in attention (6%), memory impairment (6%), asthenia (5%), blurred vision (5%), gait disturbance (4%), aphasia (4%), dysarthria (4%), and balance disorder (4%). In most cases the reactions were of mild or moderate intensity.

Pigment changes (discolouration) of ocular tissues, including the retina, have been commonly observed after several years of treatment. Some of these reports have been associated with visual impairment. Blue-grey discolouration of the nails, lips and/or skin have been commonly observed, generally at higher doses and after several years of treatment (see Precautions).

Other adverse reactions reported in these 3 studies in <2% of patients treated with TROBALT and numerically greater than placebo were increased appetite, hallucinations, myoclonus, peripheral oedema, hypokinesia, dry mouth, dysphagia, hyperhydrosis, urinary retention, malaise, and increased liver enzymes.

Most of the adverse reactions appear to be dose related (especially those classified as psychiatric and nervous system symptoms), including dizziness, somnolence, confusional state, tremor, abnormal coordination, memory impairment, blurred vision, gait disturbance, aphasia, balance disorder, constipation, dysuria, and chromaturia.

Post-marketing data

There are no relevant data available.

DOSAGE AND ADMINISTRATION

TROBALT should be initiated by a neurologist. Patients being considered for TROBALT treatment must undergo an ophthalmological examination prior to commencement of treatment. Ophthalmological examinations are required at least every six months for patients continuing treatment. If retinal pigmentation changes develop TROBALT should be discontinued unless no other treatment options are available (see PRECAUTIONS).

TROBALT must be taken orally in three divided doses each day. It may be taken with or without food (see Pharmacokinetics – Absorption). The tablets should be swallowed whole, and not chewed, crushed or divided.

To minimise the risk of adverse reactions, TROBALT must be titrated to reach an effective dose.

If a patient misses one dose or more, it is recommended that they take a single dose as soon as they remember.

After taking a missed dose, at least 3 hours should be left before the next dose and then the normal dosing schedule should be resumed.

Adults (18 to 64 years of age)

The maximum total daily starting dose is 300 mg (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. An effective maintenance dose is expected to be between 600 mg/day and 1200 mg/day.

The maximum total maintenance dose is 1200 mg/day. The safety and efficacy of doses higher than 1200 mg/day have not been established.

When withdrawing TROBALT, the dose must be gradually reduced (see Precautions).

Children and adolescents (below 18 years of age)

The safety and efficacy of TROBALT have not been established in patients below 18 years of age, therefore TROBALT is not recommended for use in this population.

Elderly (65 years of age and above)

There are only limited data on the safety and efficacy of TROBALT in patients aged 65 years and above. A reduction in the initial and the maximum maintenance dose of TROBALT is recommended in elderly patients. Doses greater than 900 mg/day are not recommended (see Pharmacokinetics – Special populations).

Renal impairment

Retigabine and its metabolites are eliminated principally by renal excretion.

No dose adjustment is required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min; see Pharmacokinetics – Renal impairment).

A 50% reduction in the initial and maintenance dose of TROBALT is recommended in patients with moderate to severe renal impairment (creatinine clearance <50 mL/min; see Pharmacokinetics – Renal impairment). The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose is increased by 50 mg every week, to a maximum total dose of 600 mg/day.

The effect of haemodialysis on retigabine clearance has not been adequately evaluated.

Hepatic impairment

No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6; see Pharmacokinetics – Hepatic impairment).

A 50% reduction in the initial and maintenance dose of TROBALT is recommended in patients with moderate or severe hepatic impairment (Child-Pugh score ≥7; see Pharmacokinetics – Hepatic impairment). The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose is increased by 50 mg every week, to a maximum total dose of 600 mg/day.

OVERDOSAGE

Symptoms and signs

There is limited experience of overdose with retigabine.

Retigabine overdoses in excess of 2500 mg/day were reported during clinical studies. In addition to adverse reactions seen at therapeutic doses, symptoms of retigabine overdose included agitation, aggressive behaviour and irritability. There were no reported sequelae.

In a study in volunteers, cardiac arrhythmia (asystole or ventricular tachycardia) occurred in two subjects within 3 hours of receiving a single 900 mg retigabine dose. The arrhythmias spontaneously resolved, and both volunteers recovered without sequelae.

Treatment

In the event of overdosage, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including ECG monitoring.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Shelf-life

18 months.

Storage

Store below 25°C.

Nature and Contents of Container

TROBALT 50 mg tablets: Purple, round, film-coated tablets, marked with “RTG 50” on one side.

TROBALT 100 mg tablets: Green, round, film-coated tablets, marked with “RTG 100” on one side.

TROBALT 200 mg tablets: Yellow, oblong, film-coated tablets, marked with “RTG-200” on one side.

TROBALT 300 mg tablets: Green, oblong, film-coated tablets, marked with “RTG-300” on one side.

TROBALT 400 mg tablets: Purple, oblong, film-coated tablets, marked with “RTG-400” on one side.

All presentations of TROBALT film-coated tablets are supplied in blister packs.

50 mg tablets: Packs containing 21, 84 or 168 film-coated tablets.

100 mg tablets: Packs containing 21, 84 or 168 film-coated tablets.

200 mg tablets: Packs containing 84 or 168 film-coated tablets.

300 mg tablets: Packs containing 84 or 168 film-coated tablets.

400 mg tablets: Packs containing 84 or 168 film-coated tablets.

Treatment initiation pack containing 21 x 50 mg film-coated tablets and 42 x 100 mg film-coated tablets.

Not all strengths or pack sizes may be distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4,
436 Johnston Street,
Abbotsford, Victoria, 3067
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

28 June 2013

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