ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of retigabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Purple, round, film-coated tablets of 5.6 mm, marked with “RTG 50” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalization in patients aged 18 years or older with epilepsy, where other appropriate combinations with other medicinal products have proved inadequate or have not been tolerated.

4.2 Posology and method of administration

Posology

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

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 1,200 mg/day.

The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established.

If patients miss 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 allowed before the next dose and then the normal dosing schedule should be resumed.

When withdrawing Trobalt, the dose must be gradually reduced over a period of at least 3 weeks (see section 4.4).

Elderly (65 years of age and above)

There are only limited data on the safety and efficacy of retigabine in patients aged 65 years and above. A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients.

The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended (see sections 4.4 and 5.2).

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 section 5.2).

A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min; see section 5.2). 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.

For patients with end-stage renal disease receiving haemodialysis, the three daily doses should be taken as usual on the dialysis day. In addition, a single supplemental dose is recommended immediately after haemodialysis. If breakthrough seizures occur towards the end of dialysis then an additional supplemental dose may be considered at the start of subsequent dialysis sessions.

Hepatic impairment

No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6; see section 5.2).

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 section 5.2). 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.

Paediatric population

The safety and efficacy of retigabine in children below 18 years of age has not yet been established (see section 5.2). Currently available pharmacokinetic data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration

Trobalt is for oral use. The tablets must be taken in three divided doses each day. The tablets should be swallowed whole, and not chewed, crushed or divided.

Trobalt may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye disorders

Pigment changes (discolouration) of ocular tissues, including the retina have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of the skin, lips or nails (see below paragraph and section 4.8). Reversibility of retinal pigmentation

after retigabine discontinuation has been reported in some subjects. The long-term prognosis of these findings is currently unknown, but some of the reports have been associated with visual impairment.

In addition a distinct form of macular abnormality with features of vitelliform maculopathy (see section 4.8) has also been identified, in most cases diagnosed with optical coherence tomography (OCT) imaging. The rate of progression of vitelliform maculopathy and its impact on retinal and macular function and vision is unclear. Vision abnormalities (field constriction, loss of central sensitivity, and reduced visual acuity) have been reported.

All patients should undergo comprehensive ophthalmological examinations at baseline and at least every six months, which should include visual acuity, slit-lamp examination, dilated fundus photography, and macular OCT imaging. If retinal pigment changes, vitelliform maculopathy or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. If continued, the patient should be monitored more closely.

Skin disorders

Pigment changes (discolouration) of the skin, lips or nails have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of ocular tissues (see above paragraph and section 4.8). In patients who develop these changes, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

Urinary retention

Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine, generally within the first 8 weeks of treatment (see section 4.8). Trobalt must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTcI) 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 disorders and hallucinations were reported in controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects.

Suicide risk

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 retigabine.

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 if signs of suicidal ideation or behaviour emerge.

Elderly (65 years of age and above)

Elderly patients 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 (see sections 4.2 and 5.2).

Withdrawal seizures

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 (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Other antiepileptic medicinal products

In vitro data indicated a low potential for interaction with other antiepileptic medicinal products (see section 5.2). The drug interaction potential was, therefore, evaluated based on a pooled analysis across clinical studies and whilst not considered as robust as stand-alone clinical interaction studies, the results support the *in vitro* data.

Based on these pooled data, retigabine did not cause clinically significant effects on the plasma trough concentrations of the following antiepileptic medicinal products:
- carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, zonisamide.

Further, based on pooled data, there were no clinically significant effects of the following antiepileptic medicinal products on retigabine pharmacokinetics:
- lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate.

This analysis also showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance.

However, steady-state data from a limited number of patients in smaller phase II studies indicated that:
- phenytoin can reduce retigabine systemic exposure by 35%
- carbamazepine can reduce retigabine systemic exposure by 33%

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.

Based on a study conducted in healthy volunteers, therapeutic doses of retigabine (600-1,200 mg/day) resulted in a minor (8-18%) increase in digoxin AUC following a single oral dose of digoxin. The increase did not appear to be dependent on retigabine dose and is not considered clinically relevant. There was no meaningful change in digoxin C_{max}. No dose adjustment of digoxin is needed.

Interaction with anaesthetics
Trobalt may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium; see section 5.1).

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 Trobalt 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 (norethindrone) components of the oral contraceptive pill. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general
Specialist advice should be given to women who are of childbearing potential. The need for treatment with antiepileptic medicinal products should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic medicine therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptic medicinal products compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to Trobalt
There are no adequate data from the use of retigabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses (see section 5.3). In a developmental study in rats whose mothers were treated with retigabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known.

Trobalt is not recommended during pregnancy and in women of childbearing age, not using contraception.

Breastfeeding

It is unknown whether retigabine is excreted in human breast milk. Animal studies have shown excretion of retagabine and/or its metabolites in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trobalt should be made taking into account the benefit of breast-feeding to the child and the benefit of Trobalt therapy to the woman.

Fertility

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 in humans at recommended doses (see section 5.3).

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

4.7 Effects on ability to drive and use machines

Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see section 4.8). 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.

4.8 Undesirable effects

Summary of the safety profile

In pooled safety data from three multicentre, randomised, double-blind, placebo-controlled studies, adverse reactions were generally mild to moderate in intensity, and were most commonly reported in the first 8 weeks of treatment. There was an apparent dose-relationship for dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation.

Adverse reactions that were most frequently reported to lead to discontinuation were dizziness, somnolence, fatigue and confusional state.

Tabulated list of adverse reactions

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
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000.

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

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Weight increased Increased appetite	
Psychiatric disorders		Confusional state Psychotic disorders Hallucinations Disorientation Anxiety	
Nervous system disorders	Dizziness Somnolence	Amnesia Aphasia Coordination abnormal Vertigo Paraesthesia Tremor Balance disorder Memory impairment Dysphasia Dysarthria Disturbance in attention Gait disturbance Myoclonus	Hypokinesia
Eye disorders	Pigment changes (discolouration) of ocular tissues, including the retina, have been observed after several years of treatment. Some of these reports have been associated with visual impairment.	Diplopia Blurred vision Acquired Vitelliform Maculopathy	
Gastrointestinal disorders		Nausea Constipation Dyspepsia Dry mouth	Dysphagia
Hepatobiliary disorders		Increased liver function tests	

System Organ Class	Very common	Common	Uncommon
Skin and subcutaneous disorders	Blue-grey discolouration of the nails, lips and/or skin have been observed, generally at higher doses and after several years of treatment.		Skin rash Hyperhidrosis
Renal and urinary disorders		Dysuria Urinary hesitation Haematuria Chromaturia	Urinary retention Nephrolithiasis
General disorders and administrative site conditions	Fatigue	Asthenia Malaise Peripheral oedema	

Description of selected adverse reactions

Adverse reactions related to voiding dysfunction, including urinary retention, were reported in 5% of retigabine-treated patients in the pooled safety dataset (see section 4.4). The majority of events occurred in the first 8 weeks of treatment, and there was no apparent dose-relationship.

In retigabine-treated patients in the pooled dataset, confusional state was reported in 9% of patients, hallucinations in 2% of patients and psychotic disorders in 1% of patients (see section 4.4). The majority of adverse reactions occurred in the first 8 weeks of treatment, and there was an apparent dose-relationship for confusional state only.
Adverse event data from clinical trial subjects showed a rate of event of discolouration of the nails, lips, skin and/or mucosa per patient year of exposure of 3.6%. The cumulative incidences of an event at 1 year, 2 years, 3 years, 4 years and 5 years of exposure are approximately 1%, 1.8%, 4.4%, 10.2% and 16.7% respectively.

Approximately 30-40% of clinical trial subjects who were being treated with retigabine and underwent a skin and/or ophthalmological examination had findings of discolouration of nails, lips, skin and/or mucosa or non-retinal ocular pigmentation, and approximately 15-30% of clinical trial subjects who were being treated with retigabine and underwent an ophthalmological examination had retinal pigmentation findings. In addition, cases of acquired vitelliform-type maculopathy have been identified, both in clinical studies and as spontaneous reports.

Data from elderly patients indicates that they may be more likely to experience certain central nervous system events, including somnolence, amnesia, coordination abnormal, vertigo, tremor, balance disorder, memory impairment and gait disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

There is limited experience of overdose with retigabine.

Retigabine overdoses in excess of 2,500 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 (cardiac arrest/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.

Management

In the event of overdose, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be as recommended by the national poisons centre, where available.

Haemodialysis has been shown to reduce the plasma concentrations of retigabine and NAMR by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX21.

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). 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 (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models, for example, in the fully kindled state and in some cases during the kindling development. 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 thiopental sodium from approximately 4 min to 53 min, and the propofol-induced sleep time from approximately 8 min to 12 min. There was no effect on sleep time induced by halothane or methohexital sodium. Retigabine may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium).

Clinical efficacy of adjunctive retigabine therapy in partial onset seizures

Three multicentre, randomized, double-blind, placebo-controlled studies in a total of 1239 adult patients have been conducted to assess the efficacy of retigabine 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 medicinal products, and more than 75% of all patients were taking ≥2 concurrent antiepileptic medicinal products. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to 12 per 28 days. Patients were randomized to placebo or retigabine at 600, 900 or 1,200 mg/day (see Table 1). During an 8-week baseline period, patients had to experience ≥4 partial onset seizures per 28 days. Patients could not be seizure-free for ≥21 days. The duration of the maintenance phase was 8 or 12 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) in all three studies
- responder rate (defined as the percentage of patients with a ≥50% reduction in 28-day total partial seizure frequency) from baseline to the maintenance phase (Studies 301 and 302 only).

Retigabine was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies (Table 1). Retigabine was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1,200 mg/day (two studies).

The studies were not designed to evaluate specific combinations of antiepileptic medicinal products. Consequently, the efficacy and safety of retigabine when taken concomitantly with antiepileptic medicinal products that were less commonly used as background treatment in the clinical studies, including levetiracetam, has not been definitely shown.

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**	**Retigabine**		
		600 mg/day	**900 mg/day**	**1,200 mg/day**
Study 205 (n=396; *n=303*)				
Total partial seizure frequency (median) % change	-13%	-23%	-29%*	-35%*
Responder rate (secondary endpoint)	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 (365 patients).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trobalt in paediatric patients aged 0 to below 2 years with Lennox Gastaut Syndrome (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Trobalt in paediatric patients aged 2 to below 18 years with Lennox Gastaut Syndrome, and in paediatric patients aged 0 to below 18 years with partial onset seizures (see section 4.2 for information on paediatric use) .

5.2 Pharmacokinetic properties

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%.

Administration of retigabine with a high fat meal resulted in no change in the overall extent of retigabine absorption, but food reduced the between-subject variability in C_{max} (23%) compared to the fasted state (41%), and led to an increase in C_{max} (38%). The effect of food on C_{max} under usual clinical conditions is not expected to be clinically relevant. Therefore Trobalt 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.

Biotransformation

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.

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.

Elimination

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose is recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (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 1,200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Special patient populations

Renal impairment
In a single-dose study, 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. Adjustment of the Trobalt dose is recommended in patients with moderate to severe renal impairment but no adjustment of the Trobalt dose is recommended in patients with mild renal impairment (see section 4.2).

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.

In a second single-dose study in subjects with end stage renal disease receiving chronic haemodialysis (n= 8), initiation of dialysis at approximately 4 hours after a single dose of retigabine (100 mg) resulted in a median reduction in retigabine plasma concentrations of 52% from the start to end of dialysis. The percentage decrease in plasma concentration during dialysis ranged from 34% to 60% except for one subject who had a 17% reduction.

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 Trobalt dose is recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Body weight
In a population pharmacokinetic analysis, retigabine clearance increased with increasing body surface area. However, this increase is not considered to be clinically meaningful, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of body weight.

Elderly (65 years of age and above)
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 section 4.2).

Gender
The results of a single-dose study showed that in young adult volunteers, retigabine C_{max} was approximately 65% higher in females than in males, and in elderly volunteers (66 to 82 years of age), retigabine C_{max} was approximately 75% higher in females compared with males. When C_{max} was normalized for weight, the values were approximately 30% higher in young females than in males and 40% higher in elderly females compared with males. However, there was no apparent gender difference in weight-normalized clearance, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of gender.

Race
A post-hoc analysis across multiple healthy volunteer studies demonstrated a 20% reduction in retigabine clearance in healthy black volunteers relative to healthy Caucasian volunteers. However, this effect is not considered clinically significant, therefore no adjustment of the Trobalt dose is recommended.

Paediatric population
The pharmacokinetics of retigabine in children below 12 years of age have not been investigated.

An open-label, multiple dose pharmacokinetic, safety and tolerability study in five subjects aged between 12 years to less than 18 years with partial onset seizures determined that the pharmacokinetics of retigabine in adolescents were consistent with the pharmacokinetics of retigabine in adults. However, efficacy and safety of retigabine have not been determined in adolescents.

5.3 Preclinical safety data

Maximum doses in repeat dose toxicity studies were limited by the exaggerated pharmacologic effects of retigabine (including ataxia, hypokinesia and tremor). At no observed effect levels, animal exposure in these studies was generally less than that reached in humans at recommended clinical doses.

Distension of the gall bladder was seen in studies with dogs, but there was no evidence of cholestasis or other signs of gall bladder dysfunction, and bile ejection volume was unchanged. The gall bladder distension in the dog resulted in focal compression of the liver. No signs of gall bladder dysfunction were seen clinically.

Non-clinical data reveal no special hazard for humans based on studies of genotoxicity or carcinogenic potential.

Reproductive toxicology

Retigabine had no effect on fertility or general reproductive performance.

In rats, retigabine and/or its metabolites crossed the placenta resulting in tissue concentrations that were similar in dams and foetuses.

There was no evidence of teratogenicity following administration of retigabine to pregnant animals during the period of organogenesis. In a study of peri- and post-natal development in rats, retigabine was associated with increased perinatal mortality following administration during pregnancy. In addition, there was a delay in auditory startle response development. These findings were apparent at exposure levels lower than those obtained with clinically recommended doses and were accompanied by maternal toxicities (including ataxia, hypokinesia, tremor and reduced body weight gain). The maternal toxicities interfered with higher dosing of the dams and hence deduction of safety margins with regard to human therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Hypromellose
Magnesium stearate
Microcrystalline cellulose.

Film-coating

50 mg tablets:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Indigo carmine aluminium lake (E132)
Carmine (E120).
Lecithin (SOY)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

50 mg tablets:
Opaque PVC-PVDC-aluminium foil blisters. Packs containing 21or 84 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/001, EU/1/11/681/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 March 2011
Date of latest renewal: 14 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of retigabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Green, round, film-coated tablets of 7.1 mm, marked with “RTG 100” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalization in patients aged 18 years or older with epilepsy, where other appropriate combinations with other medicinal products have proved inadequate or have not been tolerated.

4.2 Posology and method of administration

Posology

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

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 1,200 mg/day.

The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established.

If patients miss 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 allowed before the next dose and then the normal dosing schedule should be resumed.

When withdrawing Trobalt, the dose must be gradually reduced over a period of at least 3 weeks (see section 4.4).

Elderly (65 years of age and above)

There are only limited data on the safety and efficacy of retigabine in patients aged 65 years and above. A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients.

The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended (see sections 4.4 and 5.2).

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 section 5.2).

A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min; see section 5.2). 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.

For patients with end-stage renal disease receiving haemodialysis, the three daily doses should be taken as usual on the dialysis day. In addition, a single supplemental dose is recommended immediately after haemodialysis. If breakthrough seizures occur towards the end of dialysis then an additional supplemental dose may be considered at the start of subsequent dialysis sessions.

Hepatic impairment

No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6; see section 5.2).

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 section 5.2). 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.

Paediatric population

The safety and efficacy of retigabine in children below 18 years of age has not yet been established (see section 5.2). Currently available pharmacokinetic data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration

Trobalt is for oral use. The tablets must be taken in three divided doses each day. The tablets should be swallowed whole, and not chewed, crushed or divided.

Trobalt may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye disorders

Pigment changes (discolouration) of ocular tissues, including the retina have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of the skin, lips or nails (see below paragraph and section 4.8). Reversibility of retinal pigmentation

after retigabine discontinuation has been reported in some subjects. The long-term prognosis of these findings is currently unknown, but some of the reports have been associated with visual impairment.

In addition a distinct form of macular abnormality with features of vitelliform maculopathy (see section 4.8) has also been identified, in most cases diagnosed with optical coherence tomography (OCT) imaging. The rate of progression of vitelliform maculopathy and its impact on retinal and macular function and vision is unclear. Vision abnormalities (field constriction, loss of central sensitivity, and reduced visual acuity) have been reported.

All patients should undergo comprehensive ophthalmological examinations at baseline and at least every six months, which should include visual acuity, slit-lamp examination, dilated fundus photography, and macular OCT imaging. If retinal pigment changes, vitelliform maculopathy or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. If continued, the patient should be monitored more closely.

Skin disorders

Pigment changes (discolouration) of the skin, lips or nails have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of ocular tissues (see above paragraph and section 4.8). In patients who develop these changes, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

Urinary retention

Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine, generally within the first 8 weeks of treatment (see section 4.8). Trobalt must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTcI) 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 disorders and hallucinations were reported in controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects.

Suicide risk

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 retigabine.

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 if signs of suicidal ideation or behaviour emerge.

Elderly (65 years of age and above)

Elderly patients 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 (see sections 4.2 and 5.2).

Withdrawal seizures

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 (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Other antiepileptic medicinal products

In vitro data indicated a low potential for interaction with other antiepileptic medicinal products (see section 5.2). The drug interaction potential was, therefore, evaluated based on a pooled analysis across clinical studies and whilst not considered as robust as stand-alone clinical interaction studies, the results support the *in vitro* data.

Based on these pooled data, retigabine did not cause clinically significant effects on the plasma trough concentrations of the following antiepileptic medicinal products:
- carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, zonisamide.

Further, based on pooled data, there were no clinically significant effects of the following antiepileptic medicinal products on retigabine pharmacokinetics:
- lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate.

This analysis also showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance.

However, steady-state data from a limited number of patients in smaller phase II studies indicated that:
- phenytoin can reduce retigabine systemic exposure by 35%
- carbamazepine can reduce retigabine systemic exposure by 33%

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.

Based on a study conducted in healthy volunteers, therapeutic doses of retigabine (600-1,200 mg/day) resulted in a minor (8-18%) increase in digoxin AUC following a single oral dose of digoxin. The increase did not appear to be dependent on retigabine dose and is not considered clinically relevant. There was no meaningful change in digoxin C_{max}. No dose adjustment of digoxin is needed.

Interaction with anaesthetics
Trobalt may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium; see section 5.1).

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 Trobalt 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 (norethindrone) components of the oral contraceptive pill. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general
Specialist advice should be given to women who are of childbearing potential. The need for treatment with antiepileptic medicinal products should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic medicine therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptic medicinal products compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to Trobalt
There are no adequate data from the use of retigabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses (see section 5.3). In a developmental study in rats whose mothers were treated with retigabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known.

Trobalt is not recommended during pregnancy and in women of childbearing age, not using contraception.

Breastfeeding

It is unknown whether retigabine is excreted in human breast milk. Animal studies have shown excretion of retagabine and/or its metabolites in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trobalt should be made taking into account the benefit of breast-feeding to the child and the benefit of Trobalt therapy to the woman.

Fertility

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 in humans at recommended doses (see section 5.3).

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

4.7 Effects on ability to drive and use machines

Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see section 4.8). 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.

4.8 Undesirable effects

Summary of the safety profile

In pooled safety data from three multicentre, randomised, double-blind, placebo-controlled studies, adverse reactions were generally mild to moderate in intensity, and were most commonly reported in the first 8 weeks of treatment. There was an apparent dose-relationship for dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation.

Adverse reactions that were most frequently reported to lead to discontinuation were dizziness, somnolence, fatigue and confusional state.

Tabulated list of adverse reactions

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
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000.

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

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Weight increased Increased appetite	
Psychiatric disorders		Confusional state Psychotic disorders Hallucinations Disorientation Anxiety	
Nervous system disorders	Dizziness Somnolence	Amnesia Aphasia Coordination abnormal Vertigo Paraesthesia Tremor Balance disorder Memory impairment Dysphasia Dysarthria Disturbance in attention Gait disturbance Myoclonus	Hypokinesia
Eye disorders	Pigment changes (discolouration) of ocular tissues, including the retina, have been observed after several years of treatment. Some of these reports have been associated with visual impairment.	Diplopia Blurred vision Acquired Vitelliform Maculopathy	
Gastrointestinal disorders		Nausea Constipation Dyspepsia Dry mouth	Dysphagia
Hepatobiliary disorders		Increased liver function tests	

System Organ Class	Very common	Common	Uncommon
Skin and subcutaneous disorders	Blue-grey discolouration of the nails, lips and/or skin have been observed, generally at higher doses and after several years of treatment.		Skin rash Hyperhidrosis
Renal and urinary disorders		Dysuria Urinary hesitation Haematuria Chromaturia	Urinary retention Nephrolithiasis
General disorders and administrative site conditions	Fatigue	Asthenia Malaise Peripheral oedema	

Description of selected adverse reactions

Adverse reactions related to voiding dysfunction, including urinary retention, were reported in 5% of retigabine-treated patients in the pooled safety dataset (see section 4.4). The majority of events occurred in the first 8 weeks of treatment, and there was no apparent dose-relationship.

In retigabine-treated patients in the pooled dataset, confusional state was reported in 9% of patients, hallucinations in 2% of patients and psychotic disorders in 1% of patients (see section 4.4). The majority of adverse reactions occurred in the first 8 weeks of treatment, and there was an apparent dose-relationship for confusional state only.

Adverse event data from clinical trial subjects showed a rate of event of discolouration of the nails, lips, skin and/or mucosa per patient year of exposure of 3.6%. The cumulative incidences of an event at 1 year, 2 years, 3 years, 4 years and 5 years of exposure are approximately 1%, 1.8%, 4.4%, 10.2% and 16.7% respectively.

Approximately 30-40% of clinical trial subjects who were being treated with retigabine and underwent a skin and/or ophthalmological examination had findings of discolouration of nails, lips, skin and/or mucosa or non-retinal ocular pigmentation, and approximately 15-30% of clinical trial subjects who were being treated with retigabine and underwent an ophthalmological examination had retinal pigmentation findings. In addition, cases of acquired vitelliform-type maculopathy have been identified, both in clinical studies and as spontaneous reports.

Data from elderly patients indicates that they may be more likely to experience certain central nervous system events, including somnolence, amnesia, coordination abnormal, vertigo, tremor, balance disorder, memory impairment and gait disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs
There is limited experience of overdose with retigabine.

Retigabine overdoses in excess of 2,500 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 (cardiac arrest/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.

Management

In the event of overdose, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be as recommended by the national poisons centre, where available.

Haemodialysis has been shown to reduce the plasma concentrations of retigabine and NAMR by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX21.

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). 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 (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models, for example, in the fully kindled state and in some cases during the kindling development. 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 thiopental sodium from approximately 4 min to 53 min, and the propofol-induced sleep time from approximately 8 min to 12 min. There was no effect on sleep time induced by halothane or methohexital sodium. Retigabine may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium).

Clinical efficacy of adjunctive retigabine therapy in partial onset seizures

Three multicentre, randomized, double-blind, placebo-controlled studies in a total of 1239 adult patients have been conducted to assess the efficacy of retigabine 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 medicinal products, and more than 75% of all patients were taking ≥2 concurrent antiepileptic medicinal products. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to 12 per 28 days. Patients were randomized to placebo or retigabine at 600, 900 or 1,200 mg/day (see Table 1). During an 8-week baseline period, patients had to experience ≥4 partial onset seizures per 28 days. Patients could not be seizure-free for ≥21 days. The duration of the maintenance phase was 8 or 12 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) in all three studies
- responder rate (defined as the percentage of patients with a ≥50% reduction in 28-day total partial seizure frequency) from baseline to the maintenance phase (Studies 301 and 302 only).

Retigabine was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies (Table 1). Retigabine was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1,200 mg/day (two studies).

The studies were not designed to evaluate specific combinations of antiepileptic medicinal products. Consequently, the efficacy and safety of retigabine when taken concomitantly with antiepileptic medicinal products that were less commonly used as background treatment in the clinical studies, including levetiracetam, has not been definitely shown.

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**	**Retigabine**		
		600 mg/day	**900 mg/day**	**1,200 mg/day**
Study 205 (n=396; *n=303*)				
Total partial seizure frequency (median) % change	-13%	-23%	-29%*	-35%*
Responder rate (secondary endpoint)	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 (365 patients).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trobalt in paediatric patients aged 0 to below 2 years with Lennox Gastaut Syndrome (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Trobalt in paediatric patients aged 2 to below 18 years with Lennox Gastaut Syndrome, and in paediatric patients aged 0 to below 18 years with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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%.

Administration of retigabine with a high fat meal resulted in no change in the overall extent of retigabine absorption, but food reduced the between-subject variability in C_{max} (23%) compared to the fasted state (41%), and led to an increase in C_{max} (38%). The effect of food on C_{max} under usual clinical conditions is not expected to be clinically relevant. Therefore Trobalt 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.

Biotransformation

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.

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.

Elimination

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose is recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (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 1,200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Special patient populations

Renal impairment
In a single-dose study, 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. Adjustment of the Trobalt dose is recommended in patients with moderate to severe renal impairment but no adjustment of the Trobalt dose is recommended in patients with mild renal impairment (see section 4.2).

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.

In a second single-dose study in subjects with end stage renal disease receiving chronic haemodialysis (n= 8), initiation of dialysis at approximately 4 hours after a single dose of retigabine (100 mg) resulted in a median reduction in retigabine plasma concentrations of 52% from the start to end of dialysis. The percentage decrease in plasma concentration during dialysis ranged from 34% to 60% except for one subject who had a 17% reduction.

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 Trobalt dose is recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Body weight
In a population pharmacokinetic analysis, retigabine clearance increased with increasing body surface area. However, this increase is not considered to be clinically meaningful, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of body weight.

Elderly (65 years of age and above)
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 section 4.2).

Gender
The results of a single-dose study showed that in young adult volunteers, retigabine C_{max} was approximately 65% higher in females than in males, and in elderly volunteers (66 to 82 years of age), retigabine C_{max} was approximately 75% higher in females compared with males. When C_{max} was normalized for weight, the values were approximately 30% higher in young females than in males and 40% higher in elderly females compared with males. However, there was no apparent gender difference in weight-normalized clearance, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of gender.

Race
A post-hoc analysis across multiple healthy volunteer studies demonstrated a 20% reduction in retigabine clearance in healthy black volunteers relative to healthy Caucasian volunteers. However, this effect is not considered clinically significant, therefore no adjustment of the Trobalt dose is recommended.

Paediatric population
The pharmacokinetics of retigabine in children below 12 years of age have not been investigated.

An open-label, multiple dose pharmacokinetic, safety and tolerability study in five subjects aged between 12 years to less than 18 years with partial onset seizures determined that the pharmacokinetics of retigabine in adolescents were consistent with the pharmacokinetics of retigabine in adults. However, efficacy and safety of retigabine have not been determined in adolescents.

5.3 Preclinical safety data

Maximum doses in repeat dose toxicity studies were limited by the exaggerated pharmacologic effects of retigabine (including ataxia, hypokinesia and tremor). At no observed effect levels, animal exposure in these studies was generally less than that reached in humans at recommended clinical doses.

Distension of the gall bladder was seen in studies with dogs, but there was no evidence of cholestasis or other signs of gall bladder dysfunction, and bile ejection volume was unchanged. The gall bladder distension in the dog resulted in focal compression of the liver. No signs of gall bladder dysfunction were seen clinically.

Non-clinical data reveal no special hazard for humans based on studies of genotoxicity or carcinogenic potential.

Reproductive toxicology

Retigabine had no effect on fertility or general reproductive performance.

In rats, retigabine and/or its metabolites crossed the placenta resulting in tissue concentrations that were similar in dams and foetuses.

There was no evidence of teratogenicity following administration of retigabine to pregnant animals during the period of organogenesis. In a study of peri- and post-natal development in rats, retigabine was associated with increased perinatal mortality following administration during pregnancy. In addition, there was a delay in auditory startle response development. These findings were apparent at exposure levels lower than those obtained with clinically recommended doses and were accompanied by maternal toxicities (including ataxia, hypokinesia, tremor and reduced body weight gain). The maternal toxicities interfered with higher dosing of the dams and hence deduction of safety margins with regard to human therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Hypromellose
Magnesium stearate
Microcrystalline cellulose.

Film-coating

100 mg tablets:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172).
Lecithin (SOY)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

100 mg tablets:
Opaque PVC-PVDC-aluminium foil blisters. Packs containing 21or 84 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/004, EU/1/11/681/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 March 2011
Date of latest renewal: 14 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of retigabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oblong, film-coated tablets of 7.1 mm x 14 mm, marked with “RTG-200” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalization in patients aged 18 years or older with epilepsy, where other appropriate combinations with other medicinal products have proved inadequate or have not been tolerated.

4.2 Posology and method of administration

Posology

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

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 1,200 mg/day.

The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established.

If patients miss 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 allowed before the next dose and then the normal dosing schedule should be resumed.

When withdrawing Trobalt, the dose must be gradually reduced over a period of at least 3 weeks (see section 4.4).

Elderly (65 years of age and above)

There are only limited data on the safety and efficacy of retigabine in patients aged 65 years and above. A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients.

The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended (see sections 4.4 and 5.2).

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 section 5.2).

A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min; see section 5.2). 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.

For patients with end-stage renal disease receiving haemodialysis, the three daily doses should be taken as usual on the dialysis day. In addition, a single supplemental dose is recommended immediately after haemodialysis. If breakthrough seizures occur towards the end of dialysis then an additional supplemental dose may be considered at the start of subsequent dialysis sessions.

Hepatic impairment

No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6; see section 5.2).

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 section 5.2). 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.

Paediatric population

The safety and efficacy of retigabine in children below 18 years of age has not yet been established (see section 5.2). Currently available pharmacokinetic data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration

Trobalt is for oral use. The tablets must be taken in three divided doses each day. The tablets should be swallowed whole, and not chewed, crushed or divided.

Trobalt may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye disorders

Pigment changes (discolouration) of ocular tissues, including the retina have been reported in long-term clinical studies withretigabine, sometimes but not always in conjunction with pigment changes of the skin, lips or nails (see below paragraph and section 4.8). Reversibility of retinal pigmentation after

retigabine discontinuation has been reported in some subjects. The long-term prognosis of these findings is currently unknown, but some of the reports have been associated with visual impairment.

In addition a distinct form of macular abnormality with features of vitelliform maculopathy (see section 4.8) has also been identified, in most cases diagnosed with optical coherence tomography (OCT) imaging. The rate of progression of vitelliform maculopathy and its impact on retinal and macular function and vision is unclear. Vision abnormalities (field constriction, loss of central sensitivity, and reduced visual acuity) have been reported.

All patients should undergo comprehensive ophthalmological examinations at baseline and at least every six months, which should include visual acuity, slit-lamp examination, dilated fundus photography, and macular OCT imaging. If retinal pigment changes, vitelliform maculopathy or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. If continued, the patient should be monitored more closely.

Skin disorders

Pigment changes (discolouration) of the skin, lips or nails have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of ocular tissues (see above paragraph and section 4.8). In patients who develop these changes, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

Urinary retention

Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine, generally within the first 8 weeks of treatment (see section 4.8). Trobalt must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTcI) 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 disorders and hallucinations were reported in controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects.

Suicide risk

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 retigabine.

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 if signs of suicidal ideation or behaviour emerge.

Elderly (65 years of age and above)

Elderly patients 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 (see sections 4.2 and 5.2).

Withdrawal seizures

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 (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Other antiepileptic medicinal products

In vitro data indicated a low potential for interaction with other antiepileptic medicinal products (see section 5.2). The drug interaction potential was, therefore, evaluated based on a pooled analysis across clinical studies and whilst not considered as robust as stand-alone clinical interaction studies, the results support the *in vitro* data.

Based on these pooled data, retigabine did not cause clinically significant effects on the plasma trough concentrations of the following antiepileptic medicinal products:
- carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, zonisamide.

Further, based on pooled data, there were no clinically significant effects of the following antiepileptic medicinal products on retigabine pharmacokinetics:
- lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate.

This analysis also showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance.

However, steady-state data from a limited number of patients in smaller phase II studies indicated that:
- phenytoin can reduce retigabine systemic exposure by 35%
- carbamazepine can reduce retigabine systemic exposure by 33%

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.

Based on a study conducted in healthy volunteers, therapeutic doses of retigabine (600-1,200 mg/day) resulted in a minor (8-18%) increase in digoxin AUC following a single oral dose of digoxin. The increase did not appear to be dependent on retigabine dose and is not considered clinically relevant. There was no meaningful change in digoxin C_{max}. No dose adjustment of digoxin is needed.

Interaction with anaesthetics

Trobalt may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium; see section 5.1).

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 Trobalt 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 (norethindrone) components of the oral contraceptive pill. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general
Specialist advice should be given to women who are of childbearing potential. The need for treatment with antiepileptic medicinal products should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic medicine therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptic medicinal products compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to Trobalt
There are no adequate data from the use of retigabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses (see section 5.3). In a developmental study in rats whose mothers were treated with retigabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known.

Trobalt is not recommended during pregnancy and in women of childbearing age, not using contraception.

Breastfeeding

It is unknown whether retigabine is excreted in human breast milk. Animal studies have shown excretion of retagabine and/or its metabolites in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trobalt should be made taking into account the benefit of breast-feeding to the child and the benefit of Trobalt therapy to the woman.

Fertility

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 in humans at recommended doses (see section 5.3).

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

4.7 Effects on ability to drive and use machines

Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see section 4.8). 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.

4.8 Undesirable effects

Summary of the safety profile

In pooled safety data from three multicentre, randomised, double-blind, placebo-controlled studies, adverse reactions were generally mild to moderate in intensity, and were most commonly reported in the first 8 weeks of treatment. There was an apparent dose-relationship for dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation.

Adverse reactions that were most frequently reported to lead to discontinuation were dizziness, somnolence, fatigue and confusional state.

Tabulated list of adverse reactions

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
Rare:	≥1/10,000 to <1/1,000
Very rare:	<1/10,000.

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

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Weight increased Increased appetite	
Psychiatric disorders		Confusional state Psychotic disorders Hallucinations Disorientation Anxiety	
Nervous system disorders	Dizziness Somnolence	Amnesia Aphasia Coordination abnormal Vertigo Paraesthesia Tremor Balance disorder Memory impairment Dysphasia Dysarthria Disturbance in attention Gait disturbance Myoclonus	Hypokinesia
Eye disorders	Pigment changes (discolouration) of ocular tissues, including the retina, have been observed after several years of treatment. Some of these reports have been associated with visual impairment.	Diplopia Blurred vision Acquired Vitelliform Maculopathy	
Gastrointestinal disorders		Nausea Constipation Dyspepsia Dry mouth	Dysphagia
Hepatobiliary disorders		Increased liver function tests	

System Organ Class	Very common	Common	Uncommon
Skin and subcutaneous disorders	Blue-grey discolouration of the nails, lips and/or skin have been observed, generally at higher doses and after several years of treatment.		Skin rash Hyperhidrosis
Renal and urinary disorders		Dysuria Urinary hesitation Haematuria Chromaturia	Urinary retention Nephrolithiasis
General disorders and administrative site conditions	Fatigue	Asthenia Malaise Peripheral oedema	

Description of selected adverse reactions

Adverse reactions related to voiding dysfunction, including urinary retention, were reported in 5% of retigabine-treated patients in the pooled safety dataset (see section 4.4). The majority of events occurred in the first 8 weeks of treatment, and there was no apparent dose-relationship.

In retigabine-treated patients in the pooled dataset, confusional state was reported in 9% of patients, hallucinations in 2% of patients and psychotic disorders in 1% of patients (see section 4.4). The majority of adverse reactions occurred in the first 8 weeks of treatment, and there was an apparent dose-relationship for confusional state only.

Adverse event data from clinical trial subjects showed a rate of event of discolouration of the nails, lips, skin and/or mucosa per patient year of exposure of 3.6%. The cumulative incidences of an event at 1 year, 2 years, 3 years, 4 years and 5 years of exposure are approximately 1%, 1.8%, 4.4%, 10.2% and 16.7% respectively.

Approximately 30-40% of clinical trial subjects who were being treated with retigabine and underwent a skin and/or ophthalmological examination had findings of discolouration of nails, lips, skin and/or mucosa or non-retinal ocular pigmentation, and approximately 15-30% of clinical trial subjects who were being treated with retigabine and underwent an ophthalmological examination had retinal pigmentation findings. In addition, cases of acquired vitelliform-type maculopathy have been identified, both in clinical studies and as spontaneous reports.

Data from elderly patients indicates that they may be more likely to experience certain central nervous system events, including somnolence, amnesia, coordination abnormal, vertigo, tremor, balance disorder, memory impairment and gait disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

There is limited experience of overdose with retigabine.

Retigabine overdoses in excess of 2,500 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 (cardiac arrest/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.

Management

In the event of overdose, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be as recommended by the national poisons centre, where available.

Haemodialysis has been shown to reduce the plasma concentrations of retigabine and NAMR by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX21.

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). 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 (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models, for example, in the fully kindled state and in some cases during the kindling development. 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 thiopental sodium from approximately 4 min to 53 min, and the propofol-induced sleep time from approximately 8 min to 12 min. There was no effect on sleep time induced by halothane or methohexital sodium. Retigabine may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium).

Clinical efficacy of adjunctive retigabine therapy in partial onset seizures

Three multicentre, randomized, double-blind, placebo-controlled studies in a total of 1239 adult patients have been conducted to assess the efficacy of retigabine 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 medicinal products, and more than 75% of all patients were taking ≥2 concurrent antiepileptic medicinal products. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to 12 per 28 days. Patients were randomized to placebo or retigabine at 600, 900 or 1,200 mg/day (see Table 1). During an 8-week baseline period, patients had to experience ≥4 partial onset seizures per 28 days. Patients could not be seizure-free for ≥21 days. The duration of the maintenance phase was 8 or 12 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) in all three studies
- responder rate (defined as the percentage of patients with a ≥50% reduction in 28-day total partial seizure frequency) from baseline to the maintenance phase (Studies 301 and 302 only).

Retigabine was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies (Table 1). Retigabine was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1,200 mg/day (two studies).

The studies were not designed to evaluate specific combinations of antiepileptic medicinal products. Consequently, the efficacy and safety of retigabine when taken concomitantly with antiepileptic medicinal products that were less commonly used as background treatment in the clinical studies, including levetiracetam, has not been definitely shown.

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**	**Retigabine**		
		600 mg/day	**900 mg/day**	**1,200 mg/day**
Study 205 (n=396; *n=303*)				
Total partial seizure frequency (median) % change	-13%	-23%	-29%*	-35%*
Responder rate (secondary endpoint)	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 (365 patients).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trobalt in paediatric patients aged 0 to below 2 years with Lennox Gastaut Syndrome (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Trobalt in paediatric patients aged 2 to below 18 years with Lennox Gastaut Syndrome, and in paediatric patients aged 0 to below 18 years with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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%.

Administration of retigabine with a high fat meal resulted in no change in the overall extent of retigabine absorption, but food reduced the between-subject variability in C_{max} (23%) compared to the fasted state (41%), and led to an increase in C_{max} (38%). The effect of food on C_{max} under usual clinical conditions is not expected to be clinically relevant. Therefore Trobalt 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.

Biotransformation

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.

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.

Elimination

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose is recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (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 1,200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Special patient populations

Renal impairment
In a single-dose study, 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. Adjustment of the Trobalt dose is recommended in patients with moderate to severe renal impairment but no adjustment of the Trobalt dose is recommended in patients with mild renal impairment (see section 4.2).

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.

In a second single-dose study in subjects with end stage renal disease receiving chronic haemodialysis (n= 8), initiation of dialysis at approximately 4 hours after a single dose of retigabine (100 mg) resulted in a median reduction in retigabine plasma concentrations of 52% from the start to end of dialysis. The percentage decrease in plasma concentration during dialysis ranged from 34% to 60% except for one subject who had a 17% reduction.

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 Trobalt dose is recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Body weight
In a population pharmacokinetic analysis, retigabine clearance increased with increasing body surface area. However, this increase is not considered to be clinically meaningful, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of body weight.

Elderly (65 years of age and above)
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 section 4.2).

Gender
The results of a single-dose study showed that in young adult volunteers, retigabine C_{max} was approximately 65% higher in females than in males, and in elderly volunteers (66 to 82 years of age), retigabine C_{max} was approximately 75% higher in females compared with males. When C_{max} was normalized for weight, the values were approximately 30% higher in young females than in males and 40% higher in elderly females compared with males. However, there was no apparent gender difference in weight-normalized clearance, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of gender.

Race
A post-hoc analysis across multiple healthy volunteer studies demonstrated a 20% reduction in retigabine clearance in healthy black volunteers relative to healthy Caucasian volunteers. However, this effect is not considered clinically significant, therefore no adjustment of the Trobalt dose is recommended.

Paediatric population
The pharmacokinetics of retigabine in children below 12 years of age have not been investigated.

An open-label, multiple dose pharmacokinetic, safety and tolerability study in five subjects aged between 12 years to less than 18 years with partial onset seizures determined that the pharmacokinetics of retigabine in adolescents were consistent with the pharmacokinetics of retigabine in adults. However, efficacy and safety of retigabine have not been determined in adolescents.

5.3 Preclinical safety data

Maximum doses in repeat dose toxicity studies were limited by the exaggerated pharmacologic effects of retigabine (including ataxia, hypokinesia and tremor). At no observed effect levels, animal exposure in these studies was generally less than that reached in humans at recommended clinical doses.

Distension of the gall bladder was seen in studies with dogs, but there was no evidence of cholestasis or other signs of gall bladder dysfunction, and bile ejection volume was unchanged. The gall bladder distension in the dog resulted in focal compression of the liver. No signs of gall bladder dysfunction were seen clinically.

Non-clinical data reveal no special hazard for humans based on studies of genotoxicity or carcinogenic potential.

Reproductive toxicology

Retigabine had no effect on fertility or general reproductive performance.

In rats, retigabine and/or its metabolites crossed the placenta resulting in tissue concentrations that were similar in dams and foetuses.

There was no evidence of teratogenicity following administration of retigabine to pregnant animals during the period of organogenesis. In a study of peri- and post-natal development in rats, retigabine was associated with increased perinatal mortality following administration during pregnancy. In addition, there was a delay in auditory startle response development. These findings were apparent at exposure levels lower than those obtained with clinically recommended doses and were accompanied by maternal toxicities (including ataxia, hypokinesia, tremor and reduced body weight gain). The maternal toxicities interfered with higher dosing of the dams and hence deduction of safety margins with regard to human therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Hypromellose
Magnesium stearate
Microcrystalline cellulose.

Film-coating

200 mg tablets:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Iron oxide yellow (E172).
Lecithin (SOY)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

200 mg tablets:
Opaque PVC-PVDC-aluminium foil blisters. Pack containing 84 film-coated tablets; multi-pack comprising 168 (2 x 84) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/007, EU/1/11/681/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 March 2011
Date of latest renewal: 14 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of retigabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Green, oblong, film-coated tablets of 7.1 mm x 16 mm, marked with "RTG-300" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalization in patients aged 18 years or older with epilepsy, where other appropriate combinations with other medicinal products have proved inadequate or have not been tolerated.

4.2 Posology and method of administration

Posology

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

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 1,200 mg/day.

The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established.

If patients miss 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 allowed before the next dose and then the normal dosing schedule should be resumed.

When withdrawing Trobalt, the dose must be gradually reduced over a period of at least 3 weeks (see section 4.4).

Elderly (65 years of age and above)

There are only limited data on the safety and efficacy of retigabine in patients aged 65 years and above. A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients.

The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended (see sections 4.4 and 5.2).

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 section 5.2).

A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min; see section 5.2). 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.

For patients with end-stage renal disease receiving haemodialysis, the three daily doses should be taken as usual on the dialysis day. In addition, a single supplemental dose is recommended immediately after haemodialysis. If breakthrough seizures occur towards the end of dialysis then an additional supplemental dose may be considered at the start of subsequent dialysis sessions.

Hepatic impairment

No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6; see section 5.2).

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 section 5.2). 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.

Paediatric population

The safety and efficacy of retigabine in children below 18 years of age has not yet been established (see section 5.2). Currently available pharmacokinetic data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration

Trobalt is for oral use. The tablets must be taken in three divided doses each day. The tablets should be swallowed whole, and not chewed, crushed or divided.

Trobalt may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye disorders

Pigment changes (discolouration) of ocular tissues, including the retina have been reported in long-term clinical studies withretigabine, sometimes but not always in conjunction with pigment changes of the skin, lips or nails (see below paragraph and section 4.8). Reversibility of retinal pigmentation after

retigabine discontinuation has been reported in some subjects. The long-term prognosis of these findings is currently unknown, but some of the reports have been associated with visual impairment.

In addition a distinct form of macular abnormality with features of vitelliform maculopathy (see section 4.8) has also been identified, in most cases diagnosed with optical coherence tomography (OCT) imaging. The rate of progression of vitelliform maculopathy and its impact on retinal and macular function and vision is unclear. Vision abnormalities (field constriction, loss of central sensitivity, and reduced visual acuity) have been reported.

All patients should undergo comprehensive ophthalmological examinations at baseline and at least every six months, which should include visual acuity, slit-lamp examination, dilated fundus photography, and macular OCT imaging. If retinal pigment changes, vitelliform maculopathy or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. If continued, the patient should be monitored more closely.

Skin disorders

Pigment changes (discolouration) of the skin, lips or nails have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of ocular tissues (see above paragraph and section 4.8). In patients who develop these changes, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

Urinary retention

Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine, generally within the first 8 weeks of treatment (see section 4.8). Trobalt must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTcI) 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 disorders and hallucinations were reported in controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects.

Suicide risk

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 retigabine.

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 if signs of suicidal ideation or behaviour emerge.

Elderly (65 years of age and above)

Elderly patients 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 (see sections 4.2 and 5.2).

Withdrawal seizures

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 (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Other antiepileptic medicinal products

In vitro data indicated a low potential for interaction with other antiepileptic medicinal products (see section 5.2). The drug interaction potential was, therefore, evaluated based on a pooled analysis across clinical studies and whilst not considered as robust as stand-alone clinical interaction studies, the results support the *in vitro* data.

Based on these pooled data, retigabine did not cause clinically significant effects on the plasma trough concentrations of the following antiepileptic medicinal products:
- carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, zonisamide.

Further, based on pooled data, there were no clinically significant effects of the following antiepileptic medicinal products on retigabine pharmacokinetics:
- lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate.

This analysis also showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance.

However, steady-state data from a limited number of patients in smaller phase II studies indicated that:
- phenytoin can reduce retigabine systemic exposure by 35%
- carbamazepine can reduce retigabine systemic exposure by 33%

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.

Based on a study conducted in healthy volunteers, therapeutic doses of retigabine (600-1,200 mg/day) resulted in a minor (8-18%) increase in digoxin AUC following a single oral dose of digoxin. The increase did not appear to be dependent on retigabine dose and is not considered clinically relevant. There was no meaningful change in digoxin C_{max}. No dose adjustment of digoxin is needed.

Interaction with anaesthetics
Trobalt may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium; see section 5.1).

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 Trobalt 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 (norethindrone) components of the oral contraceptive pill. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general
Specialist advice should be given to women who are of childbearing potential. The need for treatment with antiepileptic medicinal products should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic medicine therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptic medicinal products compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to Trobalt
There are no adequate data from the use of retigabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses (see section 5.3). In a developmental study in rats whose mothers were treated with retigabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known.

Trobalt is not recommended during pregnancy and in women of childbearing age, not using contraception.

Breastfeeding

It is unknown whether retigabine is excreted in human breast milk. Animal studies have shown excretion of retagabine and/or its metabolites in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trobalt should be made taking into account the benefit of breast-feeding to the child and the benefit of Trobalt therapy to the woman.

Fertility

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 in humans at recommended doses (see section 5.3).

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

4.7 Effects on ability to drive and use machines

Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see section 4.8). 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.

4.8 Undesirable effects

Summary of the safety profile

In pooled safety data from three multicentre, randomised, double-blind, placebo-controlled studies, adverse reactions were generally mild to moderate in intensity, and were most commonly reported in the first 8 weeks of treatment. There was an apparent dose-relationship for dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation.

Adverse reactions that were most frequently reported to lead to discontinuation were dizziness, somnolence, fatigue and confusional state.

Tabulated list of adverse reactions

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
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000.

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

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Weight increased Increased appetite	
Psychiatric disorders		Confusional state Psychotic disorders Hallucinations Disorientation Anxiety	
Nervous system disorders	Dizziness Somnolence	Amnesia Aphasia Coordination abnormal Vertigo Paraesthesia Tremor Balance disorder Memory impairment Dysphasia Dysarthria Disturbance in attention Gait disturbance Myoclonus	Hypokinesia
Eye disorders	Pigment changes (discolouration) of ocular tissues, including the retina, have been observed after several years of treatment. Some of these reports have been associated with visual impairment.	Diplopia Blurred vision Acquired Vitelliform Maculopathy	
Gastrointestinal disorders		Nausea Constipation Dyspepsia Dry mouth	Dysphagia
Hepatobiliary disorders		Increased liver function tests	

System Organ Class	Very common	Common	Uncommon
Skin and subcutaneous disorders	Blue-grey discolouration of the nails, lips and/or skin have been observed, generally at higher doses and after several years of treatment.		Skin rash Hyperhidrosis
Renal and urinary disorders		Dysuria Urinary hesitation Haematuria Chromaturia	Urinary retention Nephrolithiasis
General disorders and administrative site conditions	Fatigue	Asthenia Malaise Peripheral oedema	

Description of selected adverse reactions

Adverse reactions related to voiding dysfunction, including urinary retention, were reported in 5% of retigabine-treated patients in the pooled safety dataset (see section 4.4). The majority of events occurred in the first 8 weeks of treatment, and there was no apparent dose-relationship.

In retigabine-treated patients in the pooled dataset, confusional state was reported in 9% of patients, hallucinations in 2% of patients and psychotic disorders in 1% of patients (see section 4.4). The majority of adverse reactions occurred in the first 8 weeks of treatment, and there was an apparent dose-relationship for confusional state only.

Adverse event data from clinical trial subjects showed a rate of event of discolouration of the nails, lips, skin and/or mucosa per patient year of exposure of 3.6%. The cumulative incidences of an event at 1 year, 2 years, 3 years, 4 years and 5 years of exposure are approximately 1%, 1.8%, 4.4%, 10.2% and 16.7% respectively.

Approximately 30-40% of clinical trial subjects who were being treated with retigabine and underwent a skin and/or ophthalmological examination had findings of discolouration of nails, lips, skin and/or mucosa or non-retinal ocular pigmentation, and approximately 15-30% of clinical trial subjects who were being treated with retigabine and underwent an ophthalmological examination had retinal pigmentation findings. In addition, cases of acquired vitelliform-type maculopathy have been identified, both in clinical studies and as spontaneous reports.

Data from elderly patients indicates that they may be more likely to experience certain central nervous system events, including somnolence, amnesia, coordination abnormal, vertigo, tremor, balance disorder, memory impairment and gait disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

There is limited experience of overdose with retigabine.

Retigabine overdoses in excess of 2,500 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 (cardiac arrest/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.

Management

In the event of overdose, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be as recommended by the national poisons centre, where available.

Haemodialysis has been shown to reduce the plasma concentrations of retigabine and NAMR by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX21.

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). 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 (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models, for example, in the fully kindled state and in some cases during the kindling development. 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 thiopental sodium from approximately 4 min to 53 min, and the propofol-induced sleep time from approximately 8 min to 12 min. There was no effect on sleep time induced by halothane or methohexital sodium. Retigabine may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium).

Clinical efficacy of adjunctive retigabine therapy in partial onset seizures

Three multicentre, randomized, double-blind, placebo-controlled studies in a total of 1239 adult patients have been conducted to assess the efficacy of retigabine 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 medicinal products, and more than 75% of all patients were taking ≥2 concurrent antiepileptic medicinal products. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to 12 per 28 days. Patients were randomized to placebo or retigabine at 600, 900 or 1,200 mg/day (see Table 1). During an 8-week baseline period, patients had to experience ≥4 partial onset seizures per 28 days. Patients could not be seizure-free for ≥21 days. The duration of the maintenance phase was 8 or 12 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) in all three studies
- responder rate (defined as the percentage of patients with a ≥50% reduction in 28-day total partial seizure frequency) from baseline to the maintenance phase (Studies 301 and 302 only).

Retigabine was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies (Table 1). Retigabine was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1,200 mg/day (two studies).

The studies were not designed to evaluate specific combinations of antiepileptic medicinal products. Consequently, the efficacy and safety of retigabine when taken concomitantly with antiepileptic medicinal products that were less commonly used as background treatment in the clinical studies, including levetiracetam, has not been definitely shown.

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**	**Retigabine**		
		600 mg/day	**900 mg/day**	**1,200 mg/day**
Study 205 (n=396; *n=303*)				
Total partial seizure frequency (median) % change	-13%	-23%	-29%*	-35%*
Responder rate (secondary endpoint)	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 (365 patients).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trobalt in paediatric patients aged 0 to below 2 years with Lennox Gastaut Syndrome (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Trobalt in paediatric patients aged 2 to below 18 years with Lennox Gastaut Syndrome, and in paediatric patients aged 0 to below 18 years with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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%.

Administration of retigabine with a high fat meal resulted in no change in the overall extent of retigabine absorption, but food reduced the between-subject variability in C_{max} (23%) compared to the fasted state (41%), and led to an increase in C_{max} (38%). The effect of food on C_{max} under usual clinical conditions is not expected to be clinically relevant. Therefore Trobalt 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.

Biotransformation

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.

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.

Elimination

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose is recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (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 1,200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Special patient populations

Renal impairment
In a single-dose study, 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. Adjustment of the Trobalt dose is recommended in patients with moderate to severe renal impairment but no adjustment of the Trobalt dose is recommended in patients with mild renal impairment (see section 4.2).

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.

In a second single-dose study in subjects with end stage renal disease receiving chronic haemodialysis (n= 8), initiation of dialysis at approximately 4 hours after a single dose of retigabine (100 mg) resulted in a median reduction in retigabine plasma concentrations of 52% from the start to end of dialysis. The percentage decrease in plasma concentration during dialysis ranged from 34% to 60% except for one subject who had a 17% reduction.

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 Trobalt dose is recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Body weight
In a population pharmacokinetic analysis, retigabine clearance increased with increasing body surface area. However, this increase is not considered to be clinically meaningful, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of body weight.

Elderly (65 years of age and above)
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 section 4.2).

Gender
The results of a single-dose study showed that in young adult volunteers, retigabine C_{max} was approximately 65% higher in females than in males, and in elderly volunteers (66 to 82 years of age), retigabine C_{max} was approximately 75% higher in females compared with males. When C_{max} was normalized for weight, the values were approximately 30% higher in young females than in males and 40% higher in elderly females compared with males. However, there was no apparent gender difference in weight-normalized clearance, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of gender.

Race
A post-hoc analysis across multiple healthy volunteer studies demonstrated a 20% reduction in retigabine clearance in healthy black volunteers relative to healthy Caucasian volunteers. However, this effect is not considered clinically significant, therefore no adjustment of the Trobalt dose is recommended.

Paediatric population
The pharmacokinetics of retigabine in children below 12 years of age have not been investigated.

An open-label, multiple dose pharmacokinetic, safety and tolerability study in five subjects aged between 12 years to less than 18 years with partial onset seizures determined that the pharmacokinetics of retigabine in adolescents were consistent with the pharmacokinetics of retigabine in adults. However, efficacy and safety of retigabine have not been determined in adolescents.

5.3 Preclinical safety data

Maximum doses in repeat dose toxicity studies were limited by the exaggerated pharmacologic effects of retigabine (including ataxia, hypokinesia and tremor). At no observed effect levels, animal exposure in these studies was generally less than that reached in humans at recommended clinical doses.

Distension of the gall bladder was seen in studies with dogs, but there was no evidence of cholestasis or other signs of gall bladder dysfunction, and bile ejection volume was unchanged. The gall bladder distension in the dog resulted in focal compression of the liver. No signs of gall bladder dysfunction were seen clinically.

Non-clinical data reveal no special hazard for humans based on studies of genotoxicity or carcinogenic potential.

Reproductive toxicology

Retigabine had no effect on fertility or general reproductive performance.

In rats, retigabine and/or its metabolites crossed the placenta resulting in tissue concentrations that were similar in dams and foetuses.

There was no evidence of teratogenicity following administration of retigabine to pregnant animals during the period of organogenesis. In a study of peri- and post-natal development in rats, retigabine was associated with increased perinatal mortality following administration during pregnancy. In addition, there was a delay in auditory startle response development. These findings were apparent at exposure levels lower than those obtained with clinically recommended doses and were accompanied by maternal toxicities (including ataxia, hypokinesia, tremor and reduced body weight gain). The maternal toxicities interfered with higher dosing of the dams and hence deduction of safety margins with regard to human therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Hypromellose
Magnesium stearate
Microcrystalline cellulose.

Film-coating

300 mg tablets:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172).
Lecithin (SOY)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

300 mg tablets:
Opaque PVC-PVDC-aluminium foil blisters. Pack containing 84 film-coated tablets; multi-pack comprising 168 (2 x 84) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/009, EU/1/11/681/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 March 2011
Date of latest renewal: 14 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of retigabine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Purple, oblong, film-coated tablets of 8.1 mm x 18 mm, marked with "RTG-400" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalization in patients aged 18 years or older with epilepsy, where other appropriate combinations with other medicinal products have proved inadequate or have not been tolerated.

4.2 Posology and method of administration

Posology

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

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 1,200 mg/day.

The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established.

If patients miss 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 allowed before the next dose and then the normal dosing schedule should be resumed.

When withdrawing Trobalt, the dose must be gradually reduced over a period of at least 3 weeks (see section 4.4).

Elderly (65 years of age and above)

There are only limited data on the safety and efficacy of retigabine in patients aged 65 years and above. A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients.

The total daily starting dose is 150 mg/day and during the titration period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended (see sections 4.4 and 5.2).

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 section 5.2).

A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min; see section 5.2). 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.

For patients with end-stage renal disease receiving haemodialysis, the three daily doses should be taken as usual on the dialysis day. In addition, a single supplemental dose is recommended immediately after haemodialysis. If breakthrough seizures occur towards the end of dialysis then an additional supplemental dose may be considered at the start of subsequent dialysis sessions.

Hepatic impairment

No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6; see section 5.2).

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 section 5.2). 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.

Paediatric population

The safety and efficacy of retigabine in children below 18 years of age has not yet been established (see section 5.2). Currently available pharmacokinetic data are described in section 5.2, but no recommendation on a posology can be made.

Method of administration

Trobalt is for oral use. The tablets must be taken in three divided doses each day. The tablets should be swallowed whole, and not chewed, crushed or divided.

Trobalt may be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Eye disorders

Pigment changes (discolouration) of ocular tissues, including the retina have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of the skin, lips or nails (see below paragraph and section 4.8). Reversibility of retinal pigmentation

after retigabine discontinuation has been reported in some subjects. The long-term prognosis of these findings is currently unknown, but some of the reports have been associated with visual impairment.

In addition a distinct form of macular abnormality with features of vitelliform maculopathy (see section 4.8) has also been identified, in most cases diagnosed with optical coherence tomography (OCT) imaging. The rate of progression of vitelliform maculopathy and its impact on retinal and macular function and vision is unclear. Vision abnormalities (field constriction, loss of central sensitivity, and reduced visual acuity) have been reported.

All patients should undergo comprehensive ophthalmological examinations at baseline and at least every six months, which should include visual acuity, slit-lamp examination, dilated fundus photography, and macular OCT imaging. If retinal pigment changes, vitelliform maculopathy or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. If continued, the patient should be monitored more closely.

Skin disorders

Pigment changes (discolouration) of the skin, lips or nails have been reported in long-term clinical studies with retigabine, sometimes but not always in conjunction with pigment changes of ocular tissues (see above paragraph and section 4.8). In patients who develop these changes, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

Urinary retention

Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine, generally within the first 8 weeks of treatment (see section 4.8). Trobalt must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised about the risk of these possible effects.

QT interval

A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTcI) 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 disorders and hallucinations were reported in controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects.

Suicide risk

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic 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 retigabine.

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 if signs of suicidal ideation or behaviour emerge.

Elderly (65 years of age and above)

Elderly patients 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 (see sections 4.2 and 5.2).

Withdrawal seizures

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 (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Other antiepileptic medicinal products

In vitro data indicated a low potential for interaction with other antiepileptic medicinal products (see section 5.2). The drug interaction potential was, therefore, evaluated based on a pooled analysis across clinical studies and whilst not considered as robust as stand-alone clinical interaction studies, the results support the *in vitro* data.

Based on these pooled data, retigabine did not cause clinically significant effects on the plasma trough concentrations of the following antiepileptic medicinal products:
- carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, zonisamide.

Further, based on pooled data, there were no clinically significant effects of the following antiepileptic medicinal products on retigabine pharmacokinetics:
- lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate.

This analysis also showed no clinically significant effect of the inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance.

However, steady-state data from a limited number of patients in smaller phase II studies indicated that:
- phenytoin can reduce retigabine systemic exposure by 35%
- carbamazepine can reduce retigabine systemic exposure by 33%

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.

Based on a study conducted in healthy volunteers, therapeutic doses of retigabine (600-1,200 mg/day) resulted in a minor (8-18%) increase in digoxin AUC following a single oral dose of digoxin. The increase did not appear to be dependent on retigabine dose and is not considered clinically relevant. There was no meaningful change in digoxin C_{max}. No dose adjustment of digoxin is needed.

Interaction with anaesthetics

Trobalt may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium; see section 5.1).

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 Trobalt 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 (norethindrone) components of the oral contraceptive pill. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general

Specialist advice should be given to women who are of childbearing potential. The need for treatment with antiepileptic medicinal products should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of antiepileptic medicine therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

The risk of congenital malformations is increased by a factor of 2 to 3 in the offspring of mothers treated with antiepileptic medicinal products compared with the expected incidence in the general population of approximately 3%. The most frequently reported defects are cleft lip, cardiovascular malformations and neural tube defects. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and therefore monotherapy should be used whenever possible.

Risk related to Trobalt

There are no adequate data from the use of retigabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses (see section 5.3). In a developmental study in rats whose mothers were treated with retigabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known.

Trobalt is not recommended during pregnancy and in women of childbearing age, not using contraception.

Breastfeeding

It is unknown whether retigabine is excreted in human breast milk. Animal studies have shown excretion of retagabine and/or its metabolites in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trobalt should be made taking into account the benefit of breast-feeding to the child and the benefit of Trobalt therapy to the woman.

Fertility

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 in humans at recommended doses (see section 5.3).

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

4.7 Effects on ability to drive and use machines

Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see section 4.8). 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.

4.8 Undesirable effects

Summary of the safety profile

In pooled safety data from three multicentre, randomised, double-blind, placebo-controlled studies, adverse reactions were generally mild to moderate in intensity, and were most commonly reported in the first 8 weeks of treatment. There was an apparent dose-relationship for dizziness, somnolence, confusional state, aphasia, coordination abnormal, tremor, balance disorder, memory impairment, gait disturbance, blurred vision and constipation.

Adverse reactions that were most frequently reported to lead to discontinuation were dizziness, somnolence, fatigue and confusional state.

Tabulated list of adverse reactions

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
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000.

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

System Organ Class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Weight increased Increased appetite	
Psychiatric disorders		Confusional state Psychotic disorders Hallucinations Disorientation Anxiety	
Nervous system disorders	Dizziness Somnolence	Amnesia Aphasia Coordination abnormal Vertigo Paraesthesia Tremor Balance disorder Memory impairment Dysphasia Dysarthria Disturbance in attention Gait disturbance Myoclonus	Hypokinesia
Eye disorders	Pigment changes (discolouration) of ocular tissues, including the retina, have been observed after several years of treatment. Some of these reports have been associated with visual impairment.	Diplopia Blurred vision Acquired Vitelliform Maculopathy	
Gastrointestinal disorders		Nausea Constipation Dyspepsia Dry mouth	Dysphagia
Hepatobiliary disorders		Increased liver function tests	

System Organ Class	Very common	Common	Uncommon
Skin and subcutaneous disorders	Blue-grey discolouration of the nails, lips and/or skin have been observed, generally at higher doses and after several years of treatment.		Skin rash Hyperhidrosis
Renal and urinary disorders		Dysuria Urinary hesitation Haematuria Chromaturia	Urinary retention Nephrolithiasis
General disorders and administrative site conditions	Fatigue	Asthenia Malaise Peripheral oedema	

Description of selected adverse reactions

Adverse reactions related to voiding dysfunction, including urinary retention, were reported in 5% of retigabine-treated patients in the pooled safety dataset (see section 4.4). The majority of events occurred in the first 8 weeks of treatment, and there was no apparent dose-relationship.

In retigabine-treated patients in the pooled dataset, confusional state was reported in 9% of patients, hallucinations in 2% of patients and psychotic disorders in 1% of patients (see section 4.4). The majority of adverse reactions occurred in the first 8 weeks of treatment, and there was an apparent dose-relationship for confusional state only.

Adverse event data from clinical trial subjects showed a rate of event of discolouration of the nails, lips, skin and/or mucosa per patient year of exposure of 3.6%. The cumulative incidences of an event at 1 year, 2 years, 3 years, 4 years and 5 years of exposure are approximately 1%, 1.8%, 4.4%, 10.2% and 16.7% respectively.

Approximately 30-40% of clinical trial subjects who were being treated with retigabine and underwent a skin and/or ophthalmological examination had findings of discolouration of nails, lips, skin and/or mucosa or non-retinal ocular pigmentation, and approximately 15-30% of clinical trial subjects who were being treated with retigabine and underwent an ophthalmological examination had retinal pigmentation findings. In addition, cases of acquired vitelliform-type maculopathy have been identified, both in clinical studies and as spontaneous reports.

Data from elderly patients indicates that they may be more likely to experience certain central nervous system events, including somnolence, amnesia, coordination abnormal, vertigo, tremor, balance disorder, memory impairment and gait disturbance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

There is limited experience of overdose with retigabine.

Retigabine overdoses in excess of 2,500 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 (cardiac arrest/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.

Management

In the event of overdose, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be as recommended by the national poisons centre, where available.

Haemodialysis has been shown to reduce the plasma concentrations of retigabine and NAMR by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX21.

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). 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 (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models, for example, in the fully kindled state and in some cases during the kindling development. 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 thiopental sodium from approximately 4 min to 53 min, and the propofol-induced sleep time from approximately 8 min to 12 min. There was no effect on sleep time induced by halothane or methohexital sodium. Retigabine may increase the duration of anaesthesia induced by some anaesthetics (for example thiopental sodium).

Clinical efficacy of adjunctive retigabine therapy in partial onset seizures

Three multicentre, randomized, double-blind, placebo-controlled studies in a total of 1239 adult patients have been conducted to assess the efficacy of retigabine 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 medicinal products, and more than 75% of all patients were taking ≥2 concurrent antiepileptic medicinal products. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to 12 per 28 days. Patients were randomized to placebo or retigabine at 600, 900 or 1,200 mg/day (see Table 1). During an 8-week baseline period, patients had to experience ≥4 partial onset seizures per 28 days. Patients could not be seizure-free for ≥21 days. The duration of the maintenance phase was 8 or 12 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) in all three studies
- responder rate (defined as the percentage of patients with a ≥50% reduction in 28-day total partial seizure frequency) from baseline to the maintenance phase (Studies 301 and 302 only).

Retigabine was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies (Table 1). Retigabine was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1,200 mg/day (two studies).

The studies were not designed to evaluate specific combinations of antiepileptic medicinal products. Consequently, the efficacy and safety of retigabine when taken concomitantly with antiepileptic medicinal products that were less commonly used as background treatment in the clinical studies, including levetiracetam, has not been definitely shown.

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**	**Retigabine**		
		600 mg/day	**900 mg/day**	**1,200 mg/day**
Study 205 (n=396; *n=303*)				
Total partial seizure frequency (median) % change	-13%	-23%	-29%*	-35%*
Responder rate (secondary endpoint)	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 (365 patients).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Trobalt in paediatric patients aged 0 to below 2 years with Lennox Gastaut Syndrome (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Trobalt in paediatric patients aged 2 to below 18 years with Lennox Gastaut Syndrome, and in paediatric patients aged 0 to below 18 years with partial onset seizures (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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%.

Administration of retigabine with a high fat meal resulted in no change in the overall extent of retigabine absorption, but food reduced the between-subject variability in C_{max} (23%) compared to the fasted state (41%), and led to an increase in C_{max} (38%). The effect of food on C_{max} under usual clinical conditions is not expected to be clinically relevant. Therefore Trobalt 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.

Biotransformation

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.

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.

Elimination

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose is recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (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 1,200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Special patient populations

Renal impairment
In a single-dose study, 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. Adjustment of the Trobalt dose is recommended in patients with moderate to severe renal impairment but no adjustment of the Trobalt dose is recommended in patients with mild renal impairment (see section 4.2).

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.

In a second single-dose study in subjects with end stage renal disease receiving chronic haemodialysis (n= 8), initiation of dialysis at approximately 4 hours after a single dose of retigabine (100 mg) resulted in a median reduction in retigabine plasma concentrations of 52% from the start to end of dialysis. The percentage decrease in plasma concentration during dialysis ranged from 34% to 60% except for one subject who had a 17% reduction.

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 Trobalt dose is recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Body weight
In a population pharmacokinetic analysis, retigabine clearance increased with increasing body surface area. However, this increase is not considered to be clinically meaningful, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of body weight.

Elderly (65 years of age and above)
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 section 4.2).

Gender
The results of a single-dose study showed that in young adult volunteers, retigabine C_{max} was approximately 65% higher in females than in males, and in elderly volunteers (66 to 82 years of age), retigabine C_{max} was approximately 75% higher in females compared with males. When C_{max} was normalized for weight, the values were approximately 30% higher in young females than in males and 40% higher in elderly females compared with males. However, there was no apparent gender difference in weight-normalized clearance, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of gender.

Race
A post-hoc analysis across multiple healthy volunteer studies demonstrated a 20% reduction in retigabine clearance in healthy black volunteers relative to healthy Caucasian volunteers. However, this effect is not considered clinically significant, therefore no adjustment of the Trobalt dose is recommended.

Paediatric population
The pharmacokinetics of retigabine in children below 12 years of age have not been investigated.

An open-label, multiple dose pharmacokinetic, safety and tolerability study in five subjects aged between 12 years to less than 18 years with partial onset seizures determined that the pharmacokinetics of retigabine in adolescents were consistent with the pharmacokinetics of retigabine in adults. However, efficacy and safety of retigabine have not been determined in adolescents.

5.3 Preclinical safety data

Maximum doses in repeat dose toxicity studies were limited by the exaggerated pharmacologic effects of retigabine (including ataxia, hypokinesia and tremor). At no observed effect levels, animal exposure in these studies was generally less than that reached in humans at recommended clinical doses.

Distension of the gall bladder was seen in studies with dogs, but there was no evidence of cholestasis or other signs of gall bladder dysfunction, and bile ejection volume was unchanged. The gall bladder distension in the dog resulted in focal compression of the liver. No signs of gall bladder dysfunction were seen clinically.

Non-clinical data reveal no special hazard for humans based on studies of genotoxicity or carcinogenic potential.

Reproductive toxicology

Retigabine had no effect on fertility or general reproductive performance.

In rats, retigabine and/or its metabolites crossed the placenta resulting in tissue concentrations that were similar in dams and foetuses.

There was no evidence of teratogenicity following administration of retigabine to pregnant animals during the period of organogenesis. In a study of peri- and post-natal development in rats, retigabine was associated with increased perinatal mortality following administration during pregnancy. In addition, there was a delay in auditory startle response development. These findings were apparent at exposure levels lower than those obtained with clinically recommended doses and were accompanied by maternal toxicities (including ataxia, hypokinesia, tremor and reduced body weight gain). The maternal toxicities interfered with higher dosing of the dams and hence deduction of safety margins with regard to human therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium
Hypromellose
Magnesium stearate
Microcrystalline cellulose.

Film-coating

400 mg tablets:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Indigo carmine aluminium lake (E132)
Carmine (E120).
Lecithin (SOY)
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

400 mg tablets:
Opaque PVC-PVDC-aluminium foil blisters. Pack containing 84 film-coated tablets; multi-pack comprising 168 (2 x 84) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/011, EU/1/11/681/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 March 2011
Date of latest renewal: 14 January 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Glaxo Wellcome S.A.
Avda Extremadura 3
Aranda de Duero
E-09400 Burgos
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety updates reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State, and also after changes to the key elements in the educational material the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch and after launch, neurologists, ophthalmologists and other healthcare professionals (according to national requirements) are provided with a physician information pack containing the following elements:

- The Summary of Product Characteristics

- A physician's guide to prescribing. When applicable, a cover letter highlighting the main changes should also be included as part of the educational materials. The physician's guide should include the following key messages:
  - The need to inform patients that TROBALT may cause or potentiate symptoms of urinary retention/urinary hesitation
  - The need to inform patients on adverse events related to QT interval prolongation
  - Caution when using TROBALT in patients with a cardiac disease or those taking medicines concomitantly known to cause QT prolongation
  - The need to inform patients that TROBALT may cause a confusional state, hallucinations and psychotic disorders and the need to comply with dose titration to minimize these risks;
  - The need to inform patients that TROBALT may cause pigment changes in ocular tissues, including the retina, and also in the skin, lips and/or nails, as well as a distinct form of macular abnormality with features of vitelliform maculopathy;
  - The need for comprehensive ophthalmological examinations including visual acuity, slit-lamp examination, dilated fundus photography and macular optical coherence tomography (OCT) imaging at treatment initiation and at least every 6 months thereafter while treatment is ongoing. If retinal pigment, vitelliform maculopathy or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. If continued, the patient should be monitored more closely.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 50 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/001
EU/1/11/681/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 50 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 50 mg film-coated tablets
retigabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 100 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/004
EU/1/11/681/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 100 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 100 mg film-coated tablets
retigabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 200 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 200 mg film-coated tablets
retigabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 300 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
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Brentford,
Middlesex,
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 300 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 300 mg film-coated tablets
retigabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 400 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 400 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 400 mg film-coated tablets
retigabine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX – MULTIPACK ONLY)

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 200 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 168 (2 packs of 84) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
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TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/008

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX – MULTIPACK ONLY)

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 300 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 168 (2 packs of 84)film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
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TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/010

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL (WITH BLUE BOX – MULTIPACK ONLY)

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 400 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 168 (2 packs of 84)film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/012

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX – MULTIPACK ONLY)

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 200 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX – MULTIPACK ONLY)

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 300 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
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TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 300 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON (WITHOUT BLUE BOX – MULTIPACK ONLY)

1. NAME OF THE MEDICINAL PRODUCT

Trobalt 400 mg film-coated tablets
retigabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg retigabine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Middlesex,
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/681/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trobalt 400 mg

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Trobalt 50 mg film-coated tablets
Trobalt 100 mg film-coated tablets
Trobalt 200 mg film-coated tablets
Trobalt 300 mg film-coated tablets
Trobalt 400 mg film-coated tablets
Retigabine

Read all of this leaflet carefully before you start taking 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 side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trobalt is and what it is used for

Trobalt contains the active substance retigabine. Trobalt is one of a group of medicines called *antiepileptics*. It works by preventing the brain overactivity that causes epileptic seizures (also called fits).

Trobalt is used to treat seizures that affect one part of the brain (partial seizure), which may or may not extend to larger areas on both sides of the brain (secondary generalisation). It is used together with other anti-epileptic medicines to treat adults who continue to experience seizures and where other combinations of antiepileptic medicines have not worked well.

2. What you need to know before you take Trobalt

Do not take Trobalt
- if you are allergic to retigabine or any of the other ingredients of Trobalt (listed in section 6).

Warnings and precautions
Talk to your doctor before taking Trobalt:
- if you are 65 years of age or above.
- if you have kidney or liver problems.

Tell your doctor if any of these applies to you. The doctor may decide to give you a reduced dose.

Look out for serious symptoms
Trobalt can cause serious side effects, including an inability to pass urine (*urinary retention*) and mental health problems. You must look out for certain symptoms while you are taking Trobalt, to reduce the risk of any problems. See 'Look out for serious symptoms' in section 4.

Discolouration of skin, nails, lips and eyes, and eye disorders caused by changes in the centre of the retina (maculopathy)
Discolouration of parts of the eye, including the retina (inside the back of the eye) has been reported in people taking Trobalt for several years (see Section 4).
Eye disorders caused by changes in the centre of the retina (maculopathy) have been reported in people taking Trobalt (see Section 4).

Your doctor should recommend that you have an eye examination before starting treatment. The eye examination should be repeated at least every six months whilst taking Trobalt. Treatment will be stopped if any problems are found unless no other suitable treatments are available. Your doctor will monitor you more closely if treatment with Trobalt is continued.

Tell your doctor if you experience any changes in vision whilst you are being treated with Trobalt.

A blue-grey discolouration of the skin, lips or nails has also been reported in people taking Trobalt for several years (See Section 4). This sometimes occurs together with discolouration of parts of the eye. If you notice such changes while taking the medicine, tell your doctor.
Your doctor will discuss with you whether treatment with Trobalt should be continued.

Heart conditions
Trobalt can affect heart rhythm. This is more likely to affect you:

- if you are taking other medicines
- if you have an existing heart problem
- if you have low potassium (*hypokalaemia*) or low magnesium (*hypomagnesaemia*) in your blood.
- if you are 65 years of age or above

Tell your doctor if any of these apply to you, or if you notice any unusual changes in your heart beat (such as beating too fast or too slow). You may need extra check-ups (including an electrocardiogram [ECG], which is a test which records the electrical activity of your heart) while you are taking Trobalt.

Thoughts of harming yourself or suicide
A small number of people being treated with antiepileptics such as Trobalt have had thoughts of harming or killing themselves. If at any time you have these thoughts,
Immediately contact your doctor.

If you need a blood or urine test
Trobalt can affect the results of some tests. If you need a blood or urine test:
Tell the person who orders the test that you are taking Trobalt.

Children and adolescents
Trobalt is not recommended for children and adolescents aged under 18. The safety and efficacy are not yet known in this age group.

Other medicines and Trobalt
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Trobalt may affect some anaesthetics (for example thiopental sodium). If you are going to have an operation under a general anaesthetic:
Tell the doctor that you are taking Trobalt, well in advance.

Trobalt with alcohol
Drinking alcohol with Trobalt can make your vision blurred. Take extra care until you know how Trobalt and alcohol affect you.

Pregnancy and breast-feeding
There is no information about the safety of Trobalt in pregnant women. Therefore Trobalt is not recommended during pregnancy.You must use a reliable method of contraception to avoid becoming pregnant while you are being treated with Trobalt.

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 discussing it with your doctor. The doctor will weigh up the benefit to you against any risk to your baby of taking Trobalt while you are pregnant.

It is not known whether the active substance of Trobalt can pass into breast-milk.
Talk to your doctor about breast-feeding while you are taking Trobalt. Your doctor will weigh up the benefit to you against any risk to your baby of taking Trobalt while you are breast-feeding.

Driving and using machines
Trobalt can make you feel dizzy or drowsy and cause double or blurred vision.
Don't drive or use machines until you know how Trobalt affects you.

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

3. How to take Trobalt

Always take this medicine exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

How much to take
The maximum starting dose of Trobalt is 100 mg, taken three times a day (a total of 300 mg a day). Your doctor may gradually adjust your dose over a few weeks so that your seizures are better controlled, and side effects are kept to a minimum. The maximum dose is 400 mg taken three times a day (a total of 1,200 mg a day). If you are over 65 years you will usually be given a reduced starting dose and your doctor may limit the maximum dose to 900 mg a day.

If you have kidney or liver problems, your doctor may give you a reduced dose of Trobalt.

Don't take any more Trobalt than your doctor has recommended. It may take a few weeks to find the right dose of Trobalt for you.

How to take
Trobalt is for oral use. Swallow the tablet whole. Don't chew, crush or split the tablet. You can take Trobalt with or without food.

If you take more Trobalt than you should
If you take too many tablets of Trobalt, you may be more likely to have side effects, or any of these symptoms:
- feeling agitated, aggressive or irritable
- effects on heart rhythm.
  Contact your doctor or pharmacist for advice if you ever take more Trobalt than you are prescribed. If possible, show them the medicine pack.

If you forget to take Trobalt
If you miss any doses, just take one dose as soon as you remember. Then leave at least 3 hours before your next dose.
Don't take more than one dose at a time to make up for missed doses. If you are not sure what to do, ask your doctor or pharmacist.

Don’t stop taking Trobalt without advice
Take Trobalt for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

If you stop taking Trobalt
If you suddenly stop taking Trobalt, your seizures may come back or get worse. Do not reduce your dose unless your doctor tells you to. To stop taking Trobalt, it is important that the dose is reduced gradually, over at least 3 weeks.

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

4. Possible side effects

Like all medicines, Trobalt can cause side effects, although not everybody gets them.

Look out for serious symptoms

Discolouration of parts of the eye, including the retina (inside the back of the eye): this can be very common in people taking Trobalt for several years.

Eye disorders caused by changes in the centre of the retina (maculopathy): this can be common in people taking Trobalt. You may become aware of blurring of your central vision and notice trouble with reading or recognizing faces. At first, these changes might not affect your sight but, over time, it may get worse.

In some cases changes to the pigmentation in the eyes may improve after you stop taking Trobalt.

Your doctor should recommend that you have an eye examination before starting treatment. The eye examination should be repeated at least every six months whilst taking Trobalt. Treatment will be stopped if any problems are found unless no other suitable treatments are available. Your doctor will monitor you more closely if treatment with Trobalt is continued.

A blue-grey discolouration of the skin, lips or nails: this is very common in people taking Trobalt for several years. This sometimes occur together with discolouration of parts of the eye. Your doctor will discuss with you whether treatment with Trobalt should be continued.

Problems passing urine
These are common in people taking Trobalt, and can lead to not being able to pass urine at all. This is most likely to happen during the first few months of treatment with Trobalt. Symptoms include:
- pain when passing urine (*dysuria*)
- difficulty in starting to urinate (*urinary hesitation*)
- not being able to pass urine (*urinary retention*).

Tell your doctor immediately if you get any of these symptoms.

Mental health problems
These are common in people taking Trobalt, and are most likely to happen during the first few months of treatment. Symptoms include:

- confusion
- psychotic disorders (severe mental health problems)
- hallucinations (seeing or hearing things that are not there).
  Tell your doctor as soon as possible if you get any of these symptoms. Your doctor may decide that Trobalt is not suitable for you.

Very common side effects
These may affect more than 1 in 10 people:

- dizziness
- drowsiness
- lack of energy.

Common side effects
These may affect up to 1 in 10 people:

- blood in the urine; abnormally coloured urine
- feeling disorientated; anxiety
- memory problems (*amnesia*)
- difficulty in reading, writing or saying what you mean, or difficulty in understanding words
- attention problems
- lack of co-ordination; spinning sensation (*vertigo*); balance problems; problems walking
- tremors; sudden jerking of muscles (*myoclonus*)
- tingling or numbness of the hands or feet
- double or blurred vision
- constipation; feeling sick (*nausea*); indigestion; dry mouth
- weight gain; increased appetite
- swelling of lower legs and feet
- feeling weak or generally unwell
- changes in liver function, which will show up in blood tests.

Uncommon side effects
These may affect up to 1 in 100 people:

- slow or reduced muscle movement
- difficulty in swallowing
- skin rash
- excessive sweating
- kidney stones.

Elderly
If you are 65 years or older, you may be more likely than a younger adult to get the following symptoms:

- drowsiness
- memory problems
- balance problems, lack of co-ordination, spinning sensation (*vertigo*), problems walking
- tremors

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Trobalt

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. This will help protect the environment.

6. Contents of the pack and other information

What Trobalt contains
The active substance is retigabine. Each tablet contains 50 mg, 100 mg, 200 mg, 300 mg or 400 mg retigabine.
The other ingredients are: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, titanium dioxide (E171) , talc (E553b), Lecithin (SOY) and Xanthan gum.

The 50 mg and 400 mg tablets also contain indigo carmine aluminium lake (E132) and carmine (E120).
The 100 mg and 300 mg tablets also contain indigo carmine aluminium lake (E132) and iron oxide yellow (E172).
The 200 mg tablets also contain iron oxide yellow (E172).

What Trobalt looks like and contents of the pack
Trobalt 50 mg film-coated tablets are purple, round and marked “RTG 50” on one side. Each pack contains blisters of 21or 84 film-coated tablets.

Trobalt 100 mg film-coated tablets are green, round and marked “RTG 100” on one side. Each pack contains blisters of 21or 84 film-coated tablets.

Trobalt 200 mg film-coated tablets are yellow, oblong and marked “RTG-200” on one side. Each pack contains blisters of 84 or 2 x 84 film-coated tablets.

Trobalt 300 mg film-coated tablets are green, oblong and marked “RTG-300” on one side. Each pack contains blisters of 84 or 2 x 84 film-coated tablets.

Trobalt 400 mg film-coated tablets are purple, oblong and marked “RTG-400” on one side. Each pack contains blisters of 84 or 2 x 84 film-coated tablets.

Not all pack sizes may be available in your country.

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Manufacturer

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

ANNEX IV

GROUNDS FOR ONE ADDITIONAL RENEWAL

GROUDS FOR ONE ADDITIONAL RENEWAL

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Trobalt remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

Eye disorders have been observed with the use of Trobalt, including pigment changes in the retina. Uncertainties about the impact of this risk on patients remain as there is a possibility of functional abnormalities associated with retinopathy including potentially severe visual impairment.

Therefore, based upon the safety profile of Trobalt the CHMP concluded that the MAH should submit one additional renewal application in 5 years.