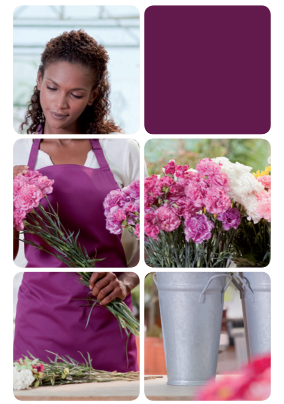
Precautions[1]

See the SmPC for more details and a full list of possible adverse events

- Caution should be exercised 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 >440 ms at baseline, an ECG should be recorded on reaching the maintenance dose
- Confusional state (9% incidence), hallucinations (2% incidence) and psychotic disorders (1% incidence) were reported in controlled clinical studies with Trobalt, generally within the first 8 weeks of treatment. Patients should be advised about the possible risk
- Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents. Available data for Trobalt do not exclude the possibility of increased risk. Patients should be monitored for signs and appropriate treatment considered. Patients and caregivers should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge
- 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
- As with other AEDs, Trobalt must be withdrawn gradually to minimise the potential for rebound seizures. It is recommended that the Trobalt dose is reduced over a period of at least 3 weeks, unless safety concerns require an abrupt withdrawal



Urinary precautions

- Trobalt targets certain potassium channels in the Kv7 family: Kv7.2 to Kv7.5, with particular affinity for neuronal channels Kv7.2 and Kv7.3[14]
- Kv7.4 and Kv7.5 are present in the smooth muscle of the bladder[15]
- Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with Trobalt, mostly within the first 8 weeks of treatment[1]
  - Trobalt must be used with caution when patients are at risk of urinary retention. It is recommended that patients are advised about the risk of these possible effects[1]

- Voiding dysfunction should be managed according to the severity of clinical symptoms (urinary retention, hesitation, bladder pain) and not post-void residual (PVR) volumes alone[16]
- The importance of seeking medical help if symptoms occur should be stressed to patients[16]

Manufacturing and pricing information

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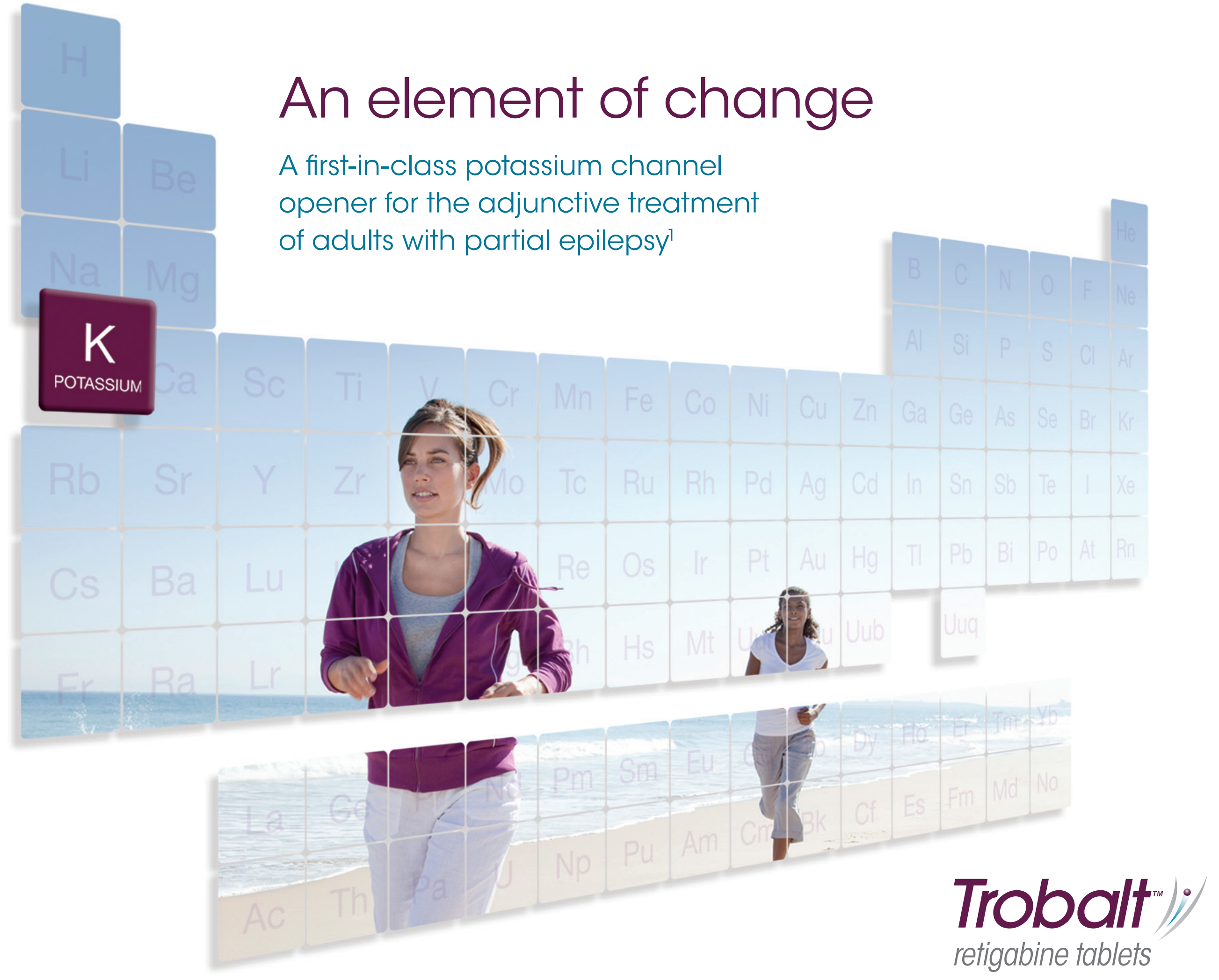
An element of change

A first-in-class potassium channel opener for the adjunctive treatment of adults with partial epilepsy[1]



Trobalt™ retigabine tablets

Prescribing Information can be found on the inside back page and in the enclosed Summary of Product Characteristics (SmPC)

Trobalt: the first K^+ channel opener for adjunctive treatment of adults with partial epilepsy[1]

- 30% of patients continue to have seizures despite current antiepileptic therapy[2]
- Trobalt is the first antiepileptic drug to target neuronal potassium channels[3-11] which have an important inhibitory role in the brain[12,13]
- Trobalt is indicated as adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy[1]

Dosing information[1]

Initiation

Trobalt is prescribed up to a maximum of 300 mg/day (100 mg three times daily)

Titration

Trobalt is increased by a maximum of 150 mg/day weekly until a therapeutic dose is reached according to the individual patient response and tolerability

Maintenance

Trobalt is effective at a dose range of 600-1200 mg/day

A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients (65 years of age and above)

A range of options is available for initiation and titration[1]

- Trobalt tablets are colour-coded and taken orally in three divided daily doses

Available doses are:

Five dose strengths and a Starter Pack enable flexibility of initiation and titration

Trobalt Starter Pack takes a patient through the first two weeks of therapy

A low potential for interactions with other AEDs[1]

See the SmPC for pharmacokinetic information

Trobalt has no clinically significant effect on plasma concentrations of the following AEDs:

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

The following AEDs have no clinically significant effect on Trobalt pharmacokinetics:

- lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate.

Phenytoin, carbamazepine and phenobarbital have no clinically signficant effect on Trobalt clearance, although phenytoin and carbamazepine can reduce Trobalt exposure by 35% and 33% respectively.

- In vitro studies showed little or no potential for Trobalt to inhibit or induce the major cytochrome P450 isoenzymes. Trobalt is unlikely to affect the pharmacokinetics of substrates of the major cytochrome P450 isoenzymes through inhibition or induction mechanisms

References:

1. Trobalt Summary of Product Characteristics. GlaxoSmithKline; 2011. **2.** World Health Organisation. Factsheet 999: Epilepsy. January 2009. http://www.who.int/mediacentre/factsheets/fs999/en/print.html Accessed 10/3/2010. **3.** Tegretol® Summary of Product Characteristics. Surrey, UK: Novartis Pharmaceuticals UK; 2009. [carbamazepine] **4.** Gabitril® Summary of Product Characteristics. Welwyn Garden City, UK: Cephalon UK (Ltd.); 2010. [tiagabine] **5.** Topamax® Summary of Product Characteristics. High Wycombe, UK: Janssen-Cilag (Ltd.); 2008. [topiramate] **6.** Epilim® Summary of Product Characteristics. Surrey, UK: Sanofi-Aventis; 2009. [valproate] **7.** Keppra® Prescribing Information. Slough, UK: UCB Pharma UK (Ltd.); 2009[levetiracetam] **8.** Lyrica® Summary of Product Information. Kent, UK: Pfizer (Ltd.); 2009. [pregabalin] **9.** Phenobarbital Summary of Product Characteristics. Uxbridge, UK: GlaxoSmithKline UK; 2009. [lamotrigine] **11.** Vimpat® Summary of Product Characteristics: Slough, UK: UCB Pharma (Ltd.); 2009. [lacosamide]. **12.** Shieh CC *et al.* Potassium channels: molecular defects, diseases, and therapeutic opportunities. *Pharmacol Rev* 2000; **52**: 557-594. **13.** Trimmer JS, Rhodes KJ. Localization of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* 2004; **66**: 477-519. **14.** Jentsch TJ. Neuronal KCNQ potassium channels: physiology and role in disease. *Nat Rev Neurosci* 2000; **1**: 21-30. **15.** Greenwood IA, Ohya S. New tricks for old dogs: KCNQ expression and role in smooth muscle. *Br J Pharmacol* 2009; **156**: 1196-1203. **16.** GlaxoSmithKline Data on File (urinary safety).

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GlaxoSmithKline

Trobalt®
retigabine tablets

Date of preparation: November 2010
NECE/EPI/0032/10