HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

02 April 2014

TROBALT 50 mg, film-coated tablets

B/21 (CIP: 34009 417 163 2 4)
B/84 (CIP: 34009 417 164 9 2)

TROBALT 100 mg, film-coated tablets

B/21 (CIP: 34009 417 165 5 3)
B/84 (CIP: 34009 417 166 1 4)

TROBALT 200 mg, film-coated tablets

B/84 (CIP: 34009 417 167 8 2)

TROBALT 300 mg, film-coated tablets

B/84 (CIP: 34009 417 168 4 3)

TROBALT 400 mg, film-coated tablets

B/84 (CIP: 34009 417 169 0 4)

TROBALT 50 mg/100 mg, film-coated tablets, treatment initiation pack

B/21 50mg tablets + B/42 100mg tablets (CIP: 34009 417 170 9 3)

Applicant: GLAXOSMITHKLINE

INN	retigabine
ATC Code (2013)	N03AX21
Reason for the request	**Re-assessment of Actual Benefit and the Improvement in Actual Benefit in response to a request by the Directorate-General for Health and the Social Security Directorate, pursuant to Article R163-19 of the French Social Security Code.**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123 2)
Indication concerned	"Trobalt is indicated as adjunctive treatment of **drug resistant** partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, **where other appropriate drug combinations have proved inadequate or have not been tolerated."**

Actual Benefit	**The actual benefit of TROBALT is <u>substantial.</u>**
Improvement in Actual Benefit	**The TROBALT proprietary medicinal-products as an adjuvant with other anti epileptics do not provide any improvement in actual benefit (level V, non existent) in the therapeutic strategy for partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.**
Therapeutic Use	**TROBALT as an adjuvant is a last-line therapeutic alternative for treating partial onset seizures with or without secondary generalisation in patients aged 18 years or older.**
Recommendations	**In order to verify the role of TROBALT in the therapeutic strategy for partial onset epilepsy, to assess treatment compliance, insofar as three daily doses are required, and treatment persistence, given the high number of treatment discontinuations in studies, the Transparency Committee repeats its request for a study originally made in its previous opinion (opinion of 6 July 2011). For adult patients treated with TROBALT, this study should describe the following:** **- the characteristics of the patients treated (socio-demographic data, type of epilepsy, duration of the disease, history, including treatment history, associated pathologies, etc.),** **- Prescribing the patterns (indication, dosage, duration of treatment, etc.) and therapeutic strategy (treatment line, co-prescriptions, etc.),** **- patient treatment compliance, treatment discontinuations and their reasons.** **The duration of the study will need to be justified by an independent scientific committee.** **Furthermore, the Transparency Committee wishes to have access to new medium- and long-term safety data (especially, urinary, neuropsychiatric and cardiac data) as soon as they are available.** **The Committee also asks for the following aspects to be monitored:** **▪ effective ophthalmologic monitoring (visual acuity, slit-lamp examination, dilated fundoscopy, visual field) for patients at the start of treatment and then at least every six months throughout the treatment.** **▪ monitoring of pigment changes in the skin and mucosa, lips and/or nails and outcome of these adverse effects if treatment is discontinued.** **The Committee recommends that the initial prescription of TROBALT be reserved for neurologists and neuropsychiatrists.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	28 March 2011 (centralised procedure) Marketing Authorisation correction of 1 July 2013: restriction of indication
Prescribing and dispensing conditions	List I

ATC Classification	2013	
	N	: Nervous system
	N03	: Antiépileptic
	N03A	: Antiépileptic
	N03AX	: Other antiépileptic
	N03AX21	: retigabine

02 BACKGROUND

In its opinion of 6 July 2011, the Transparency Committee considered the Actual Benefit of TROBALT to be substantial and that it did not provide any Improvement in Actual Benefit in the second-line treatment (i.e., after failure of at least two successive monotherapies) for partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy in combination with another antiepileptic.
In this indication, TROBALT is included on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services.

Pharmacovigilance data, reporting cases of pigment changes in ocular tissues, including the retina (one case of retinal atrophy reported) and the skin, lips and/or nails have lead to changes in the Marketing Authorisation for TROBALT by the EMA (1 July 2013). These changes relate to a restriction of indication, stronger treatment surveillance measures and additional warnings and precautions for use (see Appendix 1).
The indication for TROBALT has been restricted to drug resistant partial onset seizures where other appropriate medicinal combinations have proved inadequate or were not tolerated.
Following these changes, the Directorate-General for Health and the Social Security Directorate asked the HAS to re-assess this proprietary medicinal product.

In its opinion of 2011, the Transparency Committee requested that a study be set up to verify the role of TROBALT in the treatment strategy for partial epilepsy, to evaluate treatment compliance, insofar as three daily doses are required, and treatment persistence, given the high number of treatment discontinuations in studies.
Due to the change in the Marketing Authorisation, this study was not implemented.

03 THERAPEUTIC INDICATION

"TROBALT is indicated as adjunctive treatment of **drug resistant** partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, **where other appropriate drug combinations have proved inadequate or have not been tolerated."**

04 DOSAGE

No dosage change was made when the SPC was updated on 01 July 2013.

"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/day (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week, according to the individual patient response and tolerability.
An effective maintenance dose is expected to be between 600 mg/day and 1200 mg/day.
The maximum total maintenance dose is 1200 mg/day. The safety and efficacy of doses higher than 1200 mg/day have not been established.
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 with TROBALT, the dose must be gradually reduced.

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).
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).
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.

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

Older people (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).

Method of administration:
TROBALT must be taken orally in three divided doses each day. It may be taken with or without food. The tablets should be swallowed whole, and not chewed, crushed or divided. "

05 THERAPEUTIC NEED

Partial onset seizures are the most common form of adult seizures (70%).[1] They represent the majority of so-called drug-resistant forms,[2] requiring the prescription of a combination of at least two antiepileptic medicines.[3]

According to the latest official ANAES [National Health Accreditation and Assessment Agency] recommendations (2004)[2], no study with a high level of proof is available to dictate the long-term antiepileptic treatment strategy. Moreover, in cases of drug combinations, the data are insufficient to allow a particular drug combination to be favoured. However, it is recommended that bitherapy be used only after at least two monotherapies have failed.
When using drug combinations, a very gradual dose increase can limit the appearance of side effects. It is recommended that epilepsy and its treatment be re-assessed at a specialist centre in the event of the failure of one or more bitherapies.

Despite a large available treatment arsenal, more than 30% of patients are uncontrolled[4,5] and have an increased risk of mortality and morbidity relative to the general population: mortality two to ten times more common[2], comorbidities (psychiatric disorders and depression, significant socio-professional impact).

Patients with drug-resistant partial epilepsy, whose quality of life may be greatly impaired, need both medical and medical-social management.

Following its restriction of indication, TROBALT is now a last-line treatment for drug-resistant partial epilepsy in adults.
Another proprietary medicinal product, SABRIL (vigabatrin), is also indicated in partial onset seizures when other appropriate treatment combinations have proved insufficient or poorly tolerated.

[1]Forsgren L, Beghi E, Oun A et al. The epidemiology of epilepsy in Europe – a systematic review. European Journal of neurology 2005, 12: 245-253
[2]ANAES. Consensus Conference. Prise en charge des épilepsies partielles pharmaco-résistantes. March 2004.
[3]Reynolds E. Treating refractory epilepsy in, adults. The choice of drug or drug combinations is bewildering. BMJ 2006; 332: 565-3.
[4]Duncan JS, Sander JW, Sisodiya SM, Walker MC, Adult Epilepsy. Lancet 2006; 367; 1087-1100.
[5]Perucca E, French J, Bialer M. Development of new antiepileptic drugs, challenges, incentives and recent advantages. Neurology, 2007; 6; 793-804.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are antiepileptics indicated as an adjuvant, in the treatment of partial onset seizures:

- **Antiepileptics indicated as an adjuvant in the treatment of partial onset seizures, when all the other appropriate therapeutic combinations have proved to be inadequate or poorly tolerated**

NAME (INN) *Company*	Indications	Date of opinion	AB	IAB (Wording)	Reimbursement
SABRIL (vigabatrin) *Sanofi-Aventis*	In combination with another antiepileptic treatment, treatment of resistant partial epilepsy, with or without secondary generalisation, when all the other appropriate therapeutic combinations have proved to be inadequate or poorly tolerated Monotherapy in the treatment of infantile spasms (West's syndrome).	Renewal of inclusion: 21/09/2011	Substantial	-	Yes

Unlike TROBALT, SABRIL is also indicated in children.

- **Antiepileptics indicated as an adjuvant in the treatment of partial onset seizures:**

NAME (INN) *Company*	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
VIMPAT* (lacosamide) *UCB*	Inclusion: 04/03/2009	Substantial	IAB V versus other available treatments. However, it does provide an additional useful treatment resource for managing these patients.	Yes
GABITRIL (tiagabine) *Teva Pharma*	Renewal of inclusion: 01/02/2012	Moderate**	Opinion of 23/10/1996: IAB IV	Yes
LYRICA (pregabalin): *Pfizer*	Inclusion: 16/03/2005	Substantial	IAB V relative to NEURONTIN and other antiepileptics indicated as an adjuvant for treating partial epilepsy.	Yes
URBANYL (clobazam) *Sanofi-Aventis*	Renewal of inclusion: 14/02/2007	Substantial	-	Yes
ZEBINIX (eslicarbazepine) *Bial Portela & Ca*	Inclusion: 22/09/2010	Substantial	In view of the absence of comparative data from other antiepileptics and of the results observed in the studies, the Transparency Committee considers that ZEBINIX, used in combination with other antiepileptics, does not provide any improvement in actual benefit (level V) in the management of adult patients with partial onset epilepsy with or without secondary generalisation.	Yes

*also available for intravenous use (form not available in community pharmacies).

** Re-assessment of AB in 2001.

- **Antiepileptics indicated in the treatment of partial epilepsy as monotherapy and or as an adjuvant:**

NAME (INN) *Company*	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
EPITOMAX (topiramate) *Janssen-Cilag*	Renewal of inclusion: 18/04/2007	Substantial	Opinion of 24/11/2004: EPITOMAX does not provide any improvement in actual benefit (level V) relative to PROPRANOLOL but broadens the range of available treatments for the basic treatment of migraines. Opinion of 16/07/2003: Moderate Improvement in Actual Benefit (level III) in current treatment of epileptic children age two or older.	Yes
KEPPRA* (levetiracetam) *UCB Pharma*	Renewal of inclusion: 17/04/2013	Substantial	Opinion of 19/07/2006: Given the low risk of pharmacokinetic interactions of levetiracetam and the pharmaceutical deficiency in third-generation antiepileptics used in children, KEPPRA administered orally provides an improvement in actual benefit of level III in the extension of indication "in epileptic patients as an adjuvant in the treatment of partial onset seizures with or without secondary generalisation in children age four or older" Opinion of 07/02/2001: The Committee only has placebo-controlled data. Due to levetiracetam's pharmacokinetic profile and safety, KEPPRA does not provide an Improvement in Actual Benefit relative to NEURONTIN but a minor improvement (level IV) relative to other antiepileptics used in combination as a second-line treatment.	Yes
LAMICTAL (lamotrigine) *GSK*	Renewal of inclusion: 02/10/2013	Substantial	IAB V	Yes
NEURONTIN (gabapentin) *Pfizer*	Renewal of inclusion: 06/06/2007	Substantial	Opinion of 04/04/2001 Children age three or older: In the absence of a comparative study, this proprietary medicinal product does not provide any improvement in actual benefit relative to EPITOMAX, tablet and LAMICTAL in the extension of indication of treating partial epilepsy in children in combination with another antiepileptic treatment.	Yes
TRILEPTAL (oxcarbazepine) *Novartis Pharma*	Renewal of inclusion: 07/09/2011	Substantial	-	Yes
ZONEGRAN (zonisamide) *Eisai*	Inclusion: 16/11/2005	Substantial	ZONEGRAN is an additional treatment in combination with other antiepileptics, but does not provide any improvement in actual benefit (level V) in the management of patients with partial onset seizures with or without secondary generalisation, given the data submitted in the dossier.	Yes
DEPAKINE* (sodium valproate) *Sanofi-Aventis*	Renewal of inclusion: 19/10/2011	Substantial	-	Yes
TEGRETOL	Renewal of	Substantial	-	Yes

(carbamazepine) *Novartis Pharma*	inclusion: 09/01/2013			
DIHYDAN (phenytoin)	Renewal of inclusion: 04/12/2013	Substantial	-	Yes
MYSOLINE (primidone)	Renewal of inclusion: 15/02/2012	Low	-	Yes
GARDENAL* (phenobarbital) *Sanofi-Aventis*	Renewal of inclusion: 19/10/2011	Substantial	-	Yes
RIVOTRIL (clonazepam) *Roche*	Renewal of inclusion: 19/10/2011	Moderate	-	Yes

*also available for intravenous use (form not available in community pharmacies)

06.2 Other health technologies

Not applicable.

◗ Conclusion

Only SABRIL is a clinically relevant comparator since it is the only antiepileptic with a Marketing Authorisation "in combination with another antiepileptic treatment, treatment of resistant partial onset seizures, with or without secondary generalisation, **only where all the other appropriate therapeutic combinations have proved to be inadequate or poorly tolerated."**

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The European Marketing Authorisation for TROBALT was granted on 28 March 2011 as part of a centralised procedure.
TROBALT is currently approved in 54 countries and sold in 33 countries.

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
European Union		
Austria	Yes	Marketing Authorisation
Germany	No	
Denmark	Yes	
Italy	Yes	
Spain	Yes	
Finland	Yes	
Great Britain	Yes	
Portugal	Yes	
Sweden	Yes	
United States	Yes	Marketing Authorisation
Canada	No	-

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for request)	06/07/2011 Inclusion (National Health Insurance and Hospital Use)
Indication	"TROBALT is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy."
Actual Benefit	TROBALT is a second-line medicine (i.e. after failure of at least two monotherapies) which must be used in combination with another antiepileptic. There are treatment alternatives. The actual benefit of TROBALT is **substantial.**
Improvement in Actual Benefit	The TROBALT proprietary medicinal products do not provide Improvement in Actual Benefit (**level V**) relative to other products as adjunctive treatment for proprietary medicinal partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy.
Studies requested	**By the Transparency Committee:** In order to verify the role of TROBALT in the therapeutic strategy for partial epilepsy, to assess treatment compliance, insofar as three daily doses are required, and treatment persistence, given the high number of treatment discontinuations in studies, the Transparency Committee would like to see a follow-up study conducted in adult patients treated with TROBALT. This study should describe: ▪ the characteristics of the patients treated (socio-demographic data, type of epilepsy, duration of the disease, history, including treatment history, associated pathologies, etc.), ▪ prescribing patterns (indication, dosage, duration of treatment, etc.) and therapeutic strategy (treatment line, co-prescriptions, etc.), ▪ patient treatment compliance, treatment discontinuations and their reasons. The duration of the study will need to be justified by an independent scientific committee. Furthermore, the Transparency Committee wishes to have access to new medium- and long-term safety data (especially, urinary, neuropsychiatric and cardiac data) as soon as they are available. **By the EMA (RMP) when Marketing Authorisation was granted:** ▪ Prospective epidemiological study on the risk of urinary retention during treatment with TROBALT, especially in patients aged 65 or older, monitoring of adverse urinary events in clinical studies, ▪ Study (in progress in 2011) concerning the effect of a more flexible dosage regimen on the risk of hallucinations, psychotic disorders and accidents secondary to the neuropsychiatric effects of TROBALT.

09 ANALYSIS OF AVAILABLE DATA

The manufacturer has provided new data concerning the efficacy and safety of TROBALT (study RGB113905). The change in the wording of the indication took place on 1 July 2013; this study, conducted from 23 July 2010 to 4 December 2012, was conducted in a population that corresponded to the old indication for TROBALT. It did not seek to specifically monitor tissue pigmentation.
There are no new clinical efficacy data in the restricted indication for TROBALT.

09.1 Efficacy

9.1.1 Study RGB113905

This study, included in the European RMP,evaluated TROBALT immediate-release, in a flexible dosage regimen, in combination with a previous monotherapy, in adults with partial onset seizures.

Purpose:

Phase IIIB open-label, non-comparative study evaluating the efficacy of immediate-release retigabine (RTG) administered with a flexible dosage regimen, in combination with a previous monotherapy, in adult epileptic patients (age 18 or older) with insufficiently controlled partial onset seizures.
This previous monotherapy should include carbamazepine/oxcarbazepine (C/O), lamotrigine (LTG), levetiracetam (LEV) or valproic acid (VPA).

Method:

Primary efficacy endpoint:
Responder rate, defined by the proportion of patients with a 50% or greater reduction in the frequency of partial onset seizures in 28 days during the retigabine treatment phase (titration period and flexible dosage-regimen maintenance phase), compared with the reference period (monotherapy) and according to the antiepileptic medicine (C/O, LTG, LEV or VPA) combined with retigabine.

Secondary efficacy endpoints:
- Responder rate, defined by the proportion of patients with a 50% or greater reduction in the frequency of partial onset seizures in 28 days during the retigabine treatment phase (titration period and flexible dosage-regimen maintenance phase) compared with the reference period (monotherapy), all treatment groups together.
- Percentage of patients with a ≥ 25%, ≥ 75% and 100% reduction in the frequency of partial onset seizures in 28 days during the retigabine treatment phase (titration period and flexible dosage regimen maintenance phase) according to the antiepileptic medicine (C/O, LTG, LEV or VPA) combined with retigabine and all groups together.
- Change in the frequency of partial onset seizures between the reference period and the treatment phase (titration period and flexible dosage-regimen maintenance phase), according to the antiepileptic medicine (C/O, LTG, LEV or VPA) combined with retigabine and all groups together.

Main inclusion criteria:
- Men or women aged 18 or above,
- Confirmed diagnosis of epilepsy characterised by simple or complex partial onset seizures with or without secondary generalisation (classification of the International League Against Epilepsy (ILAE) of 1981) occurring for more than 24 weeks before the reference period.
- Having at least four partial onset seizures during the 8-week (56 day) prospective reference period with at least one partial onset seizure during each 4-week (28 day) period.
- Currently receiving a stable dose of one of the following antiepileptic medicines: carbamazepine/oxcarbazepine, lamotrigine, levetiracetam or valproic acid. The dosage of the antiepileptic medicine must have been stable for 4 weeks before starting to collect the number of seizures (retrospective or prospective) for the reference period, as well as during the reference period.

Course of the study: After a maximum screening period of 2 weeks, the subjects entered an initial phase (reference period: monotherapy by C/O, LTG, LEV or VPA) for 8 weeks in order to determine the frequency of seizures. At the end of the initial phase, the subjects included started in the retigabine treatment period (4 weeks of titration, 16 weeks for the flexible dosage-regimen maintenance period) combined with the initial monotherapy.

Treatment: All eligible subjects received retigabine (RTG) at 150 mg/day (50 mg three times daily) in combination with the reference period treatment (monotherapy). The patients underwent an RTG titration phase for 4 weeks (increase by 150 mg steps each week) up to the dosage of 600 mg/day.

RTG was then maintained between 300 and 1200 mg/day for 16 weeks, according to the response and the subject's tolerance (flexible dosage maintenance period).

Results:

The analysis of results is only descriptive (open-label, non comparative study).
A total of 203 patients were included in the study. The median dose of retigabine was 600 mg/day in the C/O, LEV and VPA groups and 700 mg/day for the LTG group during the retigabine flexible-dosage maintenance phase.

- ***Primary endpoint*** *(see Table 1):*

The highest rate of responders (ITT population, n = 200) was observed in the VPA group (56.9%) and the lowest in the LTG group (32.0%).

Table 1: Primary efficacy endpoint

	C/O (n = 55)	LTG (n = 50)	LEV (n = 44)	VPA (n = 51)	Total (n=200)
Primary efficacy endpoint N (%)	22 (40.0%)	16 (32.0%)	22 (50.0%)	29 (56.9%)	89 (44.5%)
95% CI	[27.1 - 52.9]	[19.1 - 44.9]	[35.2 - 64.8]	[43.3 - 70.5]	[37.6 - 51.4]

It is noted in the clinical study report that the differences between the rate of responders in the treatment groups could be influenced by the variable distribution of the subjects among the sites (85% of patients of the VPA group were in only two countries).

- ***Secondary endpoints:***

For all groups combined, the rate of responders (reduction ≥ 50% of the number of partial onset seizures) during the retigabine treatment phase was 44.5%.
Forty patients (20% of subjects) had a reduction of 75% to 100% of the number of partial onset seizures in 28 days during the treatment phase compared with the reference period (monotherapy), 24.5% of patients had a reduction of 50% to 75% and 38.5% of patients had a reduction of less than 50%. Thirty four patients (17%) did not have any reduction or had an increase in the frequency of seizures.
The median percentage of variation in the partial seizure frequency between the reference period and the treatment period was comparable in the four treatment groups (median reduction of 24% to 59% of the number of partial onset seizures).

09.2 Safety/Adverse effects

9.2.1 Safety

9.2.1.1 Study RGB113905

No specific monitoring of tissue pigmentation adverse effects was planned in this study (23/07/2010 to 04/12/2012).

Results:
Seventy five percent (n = 152) of the patients had an adverse event on treatment. In 70% (n = 143), these adverse events were considered to be treatment-related by the investigators.
The subjects of the C/O group reported the highest incidence of treatment-related adverse effects:

- C/O group: n = 44/56, (79%)
- LTG group: n = 37/51, (73%)
- LEV group: n = 30/44, (68%)
- VPA group: n = 32/52, (62%)

Among the adverse events considered to be treatment related, all groups of antiepileptics combined, the most common (≥ 10% of subjects) were feelings of vertigo (n = 50, 25% of patients) and drowsiness (n = 41, 20% of patients).

Nine subjects (4.5%) reported a total of 14 serious adverse events (SAE), including 4 subjects in the LTG group, 4 in the LEV group and 1 in the VPA group. Among these SAEs, convulsions, partial onset seizures and status epilepticus were considered to be treatment-related by the investigators.

Thirty-five patients (17%) left the study due to the occurrence of adverse events: 11% during the titration phase and 6% during the maintenance period (flexible RTG dosage). The main adverse effects that led to treatment discontinuation were: drowsiness, dizziness, vertigo and fatigue.
Withdrawals from the study for adverse events were more common in the LEV (25%, n = 11/44) and C/O (21%, n = 12/56) groups than in the LTG (16%, n = 8/51) and VPA (8%, n = 4/52) groups.

In comparison with other studies already published on the safety of retigabine, there have been no new signals in this study on the following safety criteria:

- Adverse events during treatment
- Vital signs (blood pressure, heart rate), weight and ECG
- American Urological Association Symptom Scale (AUA SS) score and measurement of post-void residual urine
- Haematological, biochemical and urinary lab tests.

9.2.2 Specific adverse effects: Tissue pigmentation

9.2.2.1 Review by the manufacturer on 12 July 2013

Tissue pigment changes:
This summary is based on data from all the clinical studies included in the clinical development plan for TROBALT. Adverse effects such as blue-grey pigmentation of the nails, lips and/or skin and mucous membranes as well as pigment changes in ocular tissues, including the retina, were collected specifically in clinical studies, particularly long-term extension studies (studies VRX RET-E22-303, VRX-RET-E22-304) and the early access programme (D-23129-3227).
The studies VRX-RET-E22-303 and VRX-RET-E22-304, open-label extension studies of two of the three studies (pivot studies 303 and 304) detailed in the previous opinion of the Transparency Committee,[6] collected data from 6 years of exposure to TROBALT.
The data from the early access programme (compassionate programme D-23129-3227) provided safety data after 10 years of exposure to TROBALT.
The EPAR (European Public Assessment Reports) of 30 May 2013,[7] provided data from these studies up to 13/09/2012. The manufacturer provided additional data (up to 12/07/2013).
On 12 July 2013, 89 cases of nail, lip, skin and/or mucosa and eye tissue pigmentation (including the retina) were documented in clinical studies. These effects occurred for a median retigabine dose of 900 mg/day (450 to 1500 mg/day). In 74% of cases, retigabine treatment was continued. These effects generally appeared after a long-term exposure with a mean onset time of 4.7 years (0.041 to 7.2 years). At this time, there is no demonstrated link with age or sex.
The cumulative probability of occurrence of the event (pigmentation of all tissues combined) at 1, 2, 3, 4 and 5 years of exposure to retigabine is 0.002; 0.006; 0.027; 0.068; 0.147.

[6] Transparency Committee, HAS, Opinion of 6 July 2011, TROBALT.
[7] CHMP (EMA) Opinion, TROBALT II-14, 30 May 2013.

Cases of pigmentation in patients included in studies PTG116878 (study suspended) and RTG114855 (study in progress, see 9.5), whose treatment periods were comprised between 2 and 18 weeks were reported by the manufacturer, suggesting that these adverse events may occur outside of long-term treatment.

According to the dossier provided by the manufacturer, cumulative exposure from the beginning of marketing to 30 June 2013 is estimated at 4305 patient-years, on the basis of IMS sales volumes with a mean maintenance dosage of 900 mg per day.

Among the seven cases spontaneously reported by the manufacturer, one patient had pigmentation of the lips and nails associated with retinal atrophy (53-year-old woman, treated with retigabine for 5 years at the maintenance dosage of 1200 mg/day; retigabine treatment was gradually discontinued).

The latest PSUR analysis (29 March 2013 – 28 September 2013) provided by the manufacturer, reports one new case of retinal pigmentation without loss of visual acuity (22-year-old man treated with retigabine for 1 year at the maintenance dose of 700 mg/day).
The outcome of the lesions in these two patients (atrophy and retinal pigmentation) is currently unknown.
Thirteen cases of skin, lip and/or nail pigment changes occurring during the corresponding follow-up period were reported in this latest PSUR.

Pigment changes in ocular tissues, including the retina:
Among patients treated with retigabine in long-term clinical studies, 133 have had an ophthalmological examination as of 12 July 2013. No evaluation before treatment initiation was performed in these studies.
Thirty cases of retinal pigment changes, including 18 with involvement of other ocular tissues, were reported (including the sclera, conjunctiva and iris). Twenty-two patients had pigmentation of other ocular tissues without retinal pigmentation.
No cases of blurred vision attributed to these ocular pigmentation defects have been reported.
Ten of these patients had visual acuity less than 20/20; the visual acuity value before use of the treatment is unknown. In four patients, one other ophthalmologic disease (strabismus, diabetic retinopathy, astigmatism) was identified. The six other patients had a visual acuity comprised between 20/25 and 20/50 in one eye or both eyes.
Furthermore, among the seven spontaneous reports recorded by the manufacturer as of 28 June 2013, one patient had lip and nail pigmentation associated with retinal atrophy.

Cases of pigment/colour changes in ocular tissues are considered to be very common adverse effects (≥ 1/10) after prolonged treatment with retigabine (SPC section 4.8 Undesirable effects).

The cause, natural history and long-term prognosis of these effects is currently unknown.

Pigment changes of the skin/mucosa, lips and/or nails:
Sixty-seven cases of nail, lip, skin and/or mucosa pigmentation have been reported in clinical studies, including 44 cases of nail discolouration, 46 cases affecting the skin (including around the eyes and the eyelids), 29 lip cases and 14 mucosa cases.
Twenty of these 67 cases also had retinal pigmentation and 12 had pigmentation changes in other ocular tissues without retinal pigmentation.
No data are available to assess these observations relative to medical history, connection with sun exposure, or the outcome after treatment discontinuation. The cause, natural history and long-term prognosis of these effects is currently unknown and the manufacturer indicates that additional investigations are ongoing.
Cases of pigment/colour changes are considered to be very common adverse effects (≥ 1/10) after prolonged treatment with retigabine. The estimated risk is 0.025 per patient/year of exposure.
Five of the seven spontaneous manufacturer reports as of 12 July 2013 concerned skin pigmentation (including one with a description of blue urine), three cases of nail pigmentation and two cases of pigmentation of the mucosa and lips.

9.2.2.2 Risk management plan (see Appendix 2)

Concerning ocular pigmentation events, measures for monitoring (ophthalmological examination, including visual acuity, slit-lamp examination and dilated fundoscopy) and management of these events were included in the SPC.
The prescriber's guide was updated in September 2013. This guide now contains information on the following adverse events: pigment changes in tissues of the eyes, skin, lips and nails, urinary retention, risk of lengthened QT interval and psychiatric disorders.

As part of the European risk management plan, monitoring and assessment of all identified and potential risks are planned, via the pharmacovigilance plan and risk minimisation activities (see Appendix 2).
Monitoring of specific adverse events with retigabine (urinary retention, lengthened QT interval, psychiatric disorders) is retained in the updated RMP.

This RMP specifically includes:

- Study RGB113905 (see 9 – Analysis of available data)
- Study RTG116158 (in progress): Open-label trial evaluating the effect of retigabine administered as an adjuvant, on bladder function and urination in adult patients with partial onset seizures.
- Study RTG113284 (suspended) to evaluate the pharmacokinetics and safety of retigabine as adjunctive treatment in subjects aged from 12 years to less than 18 years with partial onset seizures or Lennox-Gastaut syndrome.
- Study RTG113388 (suspended) monitoring the long-term safety of retigabine in the paediatric population (aged 12 or older) with partial epilepsy or Lennox-Gastaut syndrome.

9.2.2.3 SPC data

The indication for TROBALT was restricted on 1 July 2013 following reported cases of pigment changes. The SPC and package leaflet for TROBALT were revised to amend the indication and include information on these risks (see Appendix 1).

Following pharmacovigilance signals concerning skin pigmentation, ophthalmological monitoring (visual acuity, slit-lamp examination and dilated fundoscopy) is now required at treatment initiation and at least every 6 months during treatment due to the possible risk of vision problems (see 4.4 Special warnings and precautions for use of the SPC).
If retinal pigmentation or vision changes, or changes in nail, lip or skin colour are detected, TROBALT treatment should only be continued after careful re-assessment of the benefit-risk ratio.

Furthermore, TROBALT appears on the list of medicines under enhanced surveillance and contains a message encouraging the reporting of adverse effects in the SPC and package leaflet.

09.3 Usage/prescription data

According to the IMS data (moving annual total autumn 2013), TROBALT is not prescribed enough to appear in this panel.
According to the GERS [Partnership to Collect and Prepare Statistics] sales data (moving annual total December 2013), the following were sold in community pharmacies between January 2013 and December 2013:

- TROBALT 50 mg (B/21 tablets): 1950 boxes
- TROBALT 50 mg (B/84 tablets): 1483 boxes
- TROBALT 100 mg (B/21 tablets): 1855 boxes
- TROBALT 100 mg (B/84 tablets): 2087 boxes
- TROBALT 200 mg (B/84 tablets): 2408 boxes
- TROBALT 300 mg (B/84 tablets): 430 boxes
- TROBALT 400 mg (B/84 tablets): 84 boxes
- TROBALT 50 mg/100 mg (treatment initiation pack): 34 boxes

Over this same period, the GERS hospital sales data are as follows:

- TROBALT 50 mg: 12,537 tablets
- TROBALT 100 mg: 10,815 tablets
- TROBALT 200 mg: 16,128 tablets
- TROBALT 300 mg: 1344 tablets
- TROBALT 400 mg: 1176 tablets

09.4 Summary & discussion

Since the previous assessment of TROBALT by the Transparency Committee, new data have been provided.

Efficacy:

The efficacy of TROBALT, in its original indication was assessed in three phase III placebo-controlled studies.[8] In these studies, the percentage of responders (defined as a reduction of at least 50% in the frequency of seizures) was:

- in study 302: 38.6% for the 600 mg/day dose, 47% for the 900 mg/day dose vs 18.9% in the placebo arm
- in study 301: 55.5% for the 1200 mg/day dose vs 22.6% in the placebo arm.

The difference vs placebo was statistically significant for each of the doses.

Study RGB113905 was conducted in patients with partial epilepsy insufficiently controlled on monotherapy with carbamazepine (or oxcarbazepine), lamotrigine, levetiracetam or sodium valproate. On treatment combining the previous monotherapy and retigabine (flexible dosage between 300 and 1200 mg/day after a 4-week titration phase), the percentage of responders was 44.5% in the total study population; this percentage was higher in the subgroup receiving sodium valproate (56.9% of responders).

There are no new clinical efficacy data in the current indication, which is now restricted to last-line treatment for resistant partial onset seizures in adults.

Safety:

Study RGB113905 does not provide any specific new safety information.
Regarding tissue pigmentation data, as of 12 July 2013 (data from clinical trials), the following have been reported: 89 cases of nail, lip, skin and/or mucosa pigmentation and pigmentation of ocular tissues, including the retina. The median dose was 900 mg/day (450 to 1500 mg/day) and the median duration of exposure was 4.7 years. In 74% of cases, TROBALT treatment was continued. The estimated risk is 0.025 per patient/year of exposure.
In 133 ophthalmological examinations performed by clinical trial investigators as of 12 July 2013, retinal pigmentation was observed in 30 patients. Among these, ten patients had visual acuity less than 20/20; the visual acuity value before use of the treatment is unknown. In four patients, one other ophthalmologic disease was identified. No case of visual acuity loss attributed to retinal pigmentation has been reported to date.
Moreover, seven spontaneous reports of abnormal pigmentation were submitted, including one case of retinal atrophy.

Cases of pigment/colour changes of integuments and ocular tissues including the retina are considered to be very common adverse effects (≥ 1/10) after prolonged treatment with retigabine.

Due to a possible risk of vision problems, a complete ophthalmological examination (including visual acuity, slit-lamp examination and dilated fundoscopy) must be conducted at treatment initiation and at least every 6 months during treatment.

09.5 Planned studies

[8]Transparency Committee Opinion, TROBALT, 6 July 2011.

The manufacturer indicates that the study requested by HAS in 2011 when TROBALT was listed is not feasible as proposed by the manufacturer in March 2013 due to the restriction of indication. The manufacturer has not submitted an amended protocol for this study.
Consequently, no data are available on the use of TROBALT as regards the following:

- Population currently treated and its demographic characteristics
- Mean dosage and distribution of the population by dosage
- Mean duration of treatment and distribution of the population by duration of treatment
- Any co-prescriptions.

In its dossier, the manufacturer indicates that they are "committed to getting back to HAS with new proposals within two months, following a new opinion from the Transparency Committee".

Three trials, particularly on safety, are in progress:

Study RTG113413 (in progress): Multicentre, open-label, long-term study evaluating the safety and tolerability of retigabine administered in adult patients with partial onset seizures (extension of study RGB113905)

Study RTG 114855 (in progress): multicentre, randomised, double-blind, parallel-group, placebo-controlled study to determine the efficacy and safety of two doses of retigabine (900 mg/day and 600 mg/day administered as an adjuvant in Asian adult patients with drug-resistant partial epilepsy.

Study RTG114873 (in progress): A multicentre, open-label study evaluating the long-term, tolerability, safety, and study of retigabine administered in Asian adults with partial onset seizures (extension of study RTG114855).

Furthermore, the paediatric investigation plan is currently suspended awaiting new pigment change data.

010 THERAPEUTIC USE

010.1 Therapeutic strategy

Epilepsy is a common disease which is clinically expressed intermittently and unpredictably by seizures. The symptoms are diverse: generalised or partial seizures with or without secondary generalisation. The age of onset of the disease, its aetiology and its prognosis vary.

According to the ANAES[9] recommendations on the therapeutic strategy for treating drug-resistant partial epilepsy (DRPE) in adults, it is recommended to use bitherapy only after failure of at least two monotherapies (grade D recommendation). It is further recommended to avoid using a combination of more than two antiepileptic medicines in DRPE treatment (grade C).
When using drug combinations, increasing the dose very gradually can limit the appearance of adverse effects and educating the patient can be beneficial regarding treatment compliance. If one or more bitherapies fail, it is recommended to re-assess the epilepsy and its treatment at a specialist centre.
According these recommendations, no study with a high level of proof is available to dictate the long-term antiepileptic treatment strategy. In cases of drug combinations, the data are insufficient to allow a particular drug combination to be preferred.

The definition of drug-resistant partial epilepsy used by the ANAES is as follows:

- Persistence of seizures
- Definitely epileptic in nature
- Sufficiently frequent or disabling
- In a compliant patient
- Continuing for at least 2 years
- A correctly prescribed antiepileptic (AE) treatment

This definition has some imprecisions and it is not currently possible to obtain a therapeutic consensus concerning, in particular, the number of antiepileptic medicines to use and the duration of use for each of them.

010.2 Role in the therapeutic strategy

The indication for TROBALT was restricted on 1 July 2013 following the occurrence of adverse effects involving pigmentation of the nails, lips, skin and/or mucosa and ocular tissues, including the retina. TROBALT is now indicated as an adjuvant in the treatment of resistant partial epilepsy, when other appropriate drug combinations proved inadequate or were not tolerated. This restriction of indication therefore changes its role in the therapeutic strategy, limiting its use to a last-line treatment for resistant partial epilepsy in adults.
There are currently no efficacy and safety clinical data for this new indication.

[9] ANAES. Consensus conference. Prise en charge des épilepsies partielles pharmaco-résistantes. March 2004.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual Benefit

◗ Epileptic seizures are symptoms of a very diverse array of diseases. Epilepsy, characterised by the – usually spontaneous – recurrence of these seizures over the medium and long term, can markedly impair patient quality of life. Currently, nearly a third of patients with partial epilepsy are drug resistant.[10]
◗ This proprietary medicinal product is intended as symptomatic treatment.
◗ The efficacy/adverse effects ratio for TROBALT is high.
◗ This medicinal product is a last resort medicine, used after failure of other alternative antiepileptics and must be used in combination with another antiepileptic.
◗ There are treatment alternatives, including only one (SABRIL, vigabatrin) that occupies the same place in the therapeutic strategy (as an adjuvant, as a last-line treatment).

Consequently, the Committee considers that the actual benefit of TROBALT is <u>substantial</u> in the Marketing Authorisation indication.

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

011.2 Improvement in actual benefit (IAB)

The TROBALT proprietary medicinal products in combination with other anti epileptics do not provide any improvement in actual benefit (level V, non existent) in the therapeutic strategy for partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.

011.3 Target population

The target population for TROBALT consists of patients age 18 or older with resistant partial epilepsy with or without secondary generalisation for whom all appropriate drug combinations have proved inadequate or have not been tolerated, i.e. as a last-line treatment.

According to Jallon P. 2004,[11] the prevalence of epilepsy in France is 5 to 7/1000; drug-resistant epilepsy represents 20% of these cases, of which 60% are partial epilepsy cases.[1]
This corresponds to a target population comprised between 39,000 and 55,000 people.
However, according to this author, the estimate of the number of people with drug-resistant partial epilepsy is hindered by two difficulties: the absence of a consensual definition of drug resistance and its randomised assessment estimated indirectly from many studies of diverse patient populations.

There are no quantitative criteria to define the last line in the treatment of resistant partial epilepsy.

[10] According to the definition of drug resistance from the Consensus conference "Treating drug-resistant partial epilepsy" of March 2004.
[11] Jallon P. Epidémiologie des épilepsies partielles pharmacorésistantes. Revue de neurologie. 2004; 160: 5S22-5S30

Consequently, the target population, restricted to the field of the new indication, cannot be assessed.

For example, the manufacturer states that the available market data on the use of TROBALT (GERS September 2013) made it possible to estimate that between 400 and 800 patients received TROBALT since its inclusion on the list for reimbursement in November 2012, or over a period of 9 months. This estimate relies on the assumption of a mean dose per patient comprised between 500 and 600 mg per day, given that no direct data on the number of patients on TROBALT are available. The number of boxes of TROBALT sold reached its maximum scarcely 6 months after it became available and just before the amendment of the SPC.
Furthermore, according to the data from the general sample of beneficiaries extrapolated to the French population,[12] the number of subjects having at least one prescription for TROBALT filled between 01 November 2012 and 31 October 2013 is estimated at 890 (95% CI [273 - 1507]).

012 COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

◗ Request for data

In order to verify the role of TROBALT in the therapeutic strategy for partial epilepsy, to evaluate treatment compliance, insofar as three daily doses are required, and treatment persistence, given the high number of treatment discontinuations in studies, the Transparency Committee repeats its request for a study originally made in its previous opinion (opinion of 6 July 2011). For adult patients treated with TROBALT, this study should make it possible to describe the following:

- the characteristics of the patients treated (socio-demographic data, type of epilepsy, duration of the disease, history, including treatment history, associated pathologies, etc.),
- prescribing patterns (indication, dosage, duration of treatment, etc.) and therapeutic strategy (treatment line, co-prescriptions, etc.),
- patient treatment compliance, treatment discontinuations and their reasons.

The duration of the study will need to be justified by an independent scientific committee.
Furthermore, the Transparency Committee wishes to have access to new medium- and long-term safety data (especially, urinary, neuropsychiatric and cardiac) as soon as they are available.

The Committee also asks for the following aspects to be monitored:

- effective ophthalmologic monitoring (visual acuity, slit-lamp examination, dilated fundoscopy, visual field) for patients at the start of treatment and then at least every six months throughout the treatment.
- monitoring of pigment changes in the skin and mucosa, lips and/or nails and outcome of these adverse effects if treatment is discontinued.

◗ Specific requests relating to reimbursement

The Committee recommends that the initial prescription of TROBALT be reserved for neurologists or neuropsychiatrists.

[12]The GSB is a representative sample of National Health Insurance beneficiaries in France. It contains anonymous information on services reimbursed, demographic characteristics of beneficiaries and chronic conditions since 2003. The GSB data was extrapolated to the French population by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries present in the GSB on 01/01/2012 (n = 602,199) in proportion to the French population on 01/01/2012 (n = 65,585,857). The extrapolation coefficient obtained is 1/108.91.

Appendix 1: Comparative table of the modified sections of the SPC for TROBALT following the amendments to the Marketing Authorisation by the EMA on 01/07/2013

TROBALT, film-coated tablet SPC of 10/09/2012	TROBALT, film-coated tablet SPC of 01/07/2013
4. CLINICAL PARTICULARS **4.1 Therapeutic indications** Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy.	**4. CLINICAL PARTICULARS** **4.1 Therapeutic indications** Trobalt is indicated as adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated.
4.2 Posology and method of administration Dosage (…) 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. The effect of haemodialysis on retigabine clearance has not been sufficiently evaluated. (…)	**4.2 Posology and method of administration** Dosage (…) 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. ~~The effect of haemodialysis on retigabine clearance has not been sufficiently evaluated.~~ (…)
4.4 Special warnings and precautions for use Urinary retention Urinary retention, dysuria and urinary hesitation were reported in controlled clinical trials 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	**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 Trobalt, sometimes but not always in conjunction with pigment changes of the skin, lips or nails (see below paragraph and section 4.8). The long-term prognosis of these findings is currently unknown, but some of the reports have been associated with visual impairment. A comprehensive ophthalmological examination (including visual acuity, slit-lamp examination, and dilated fundoscopy) should be performed at baseline and at least every 6 months thereafter while treatment is ongoing. If retinal pigment or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks. Trobalt should be discontinued unless no other suitable treatment options are available. 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 TROBALT, 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,

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 drugs 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 Trobalt. 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. Older people (65 years of age and above) Older 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 As with other antiepileptic drugs, 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.	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 drugs 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 Trobalt. 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. Older people (65 years of age and above) Older 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 As with other antiepileptic drugs, 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.

4.5 Interaction with other medicinal products and other forms of interaction

(…)

Interaction with digoxin

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

Interaction with anaesthetics

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

Interaction with ethanol

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.

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 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 Trobalt (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 Trobalt dose and is not considered clinically relevant. There was no meaningful change in digoxin Cmax. 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

Coadministration 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.

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.

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.

4.8 Undesirable effects

System Organ	Very	Common	Uncommon

4.8 Undesirable effects

Classes de systèmes d'organes	Très fréquent	Fréquent	Peu fréquent
Troubles du métabolisme et de la nutrition		Prise de poids Augmentation de l'appétit	
Affections psychiatriques		Etat confusionnel Troubles psychotiques Hallucinations Désorientation Anxiété	

Class	Common		
Metabolism and nutrition disorders		Weight increased Increased appetite	
Psychiatric disorders		Confusional state Psychiatric disorders Hallucinations Disorientation Anxiety	
Nervous system disorders	Dizziness Somnolence[1]	Amnesia[1] Aphasia Coordination abnormal[1] Vertigo[1] Paraesthesia Tremor[1] Balance disorder[1] Memory impairment[1] Dysphasia Dysarthria Disturbance in attention Gait disturbance[1] Myoclonus	Hypokinesia
Eye disorders		Diplopia Blurred vision	
Gastrointestinal disorders		Nausea Constipation Dyspepsia Dry mouth	Dysphagia
Hepatobiliary disorders		Abnormal (increased) liver function tests	
Skin and subcutaneous tissue disorders			Skin rash Hyperhidrosis
Renal and urinary disorders		Dysuria Urinary hesitation Haematuria Chromaturia	Urinary retention Nephrolithiasis
General disorders and administration site conditions	Fatigue	Asthenia Malaise Peripheral oedema	

Affections du système nerveux	Sensations vertigineuses Somnolence[1]	Amnésie[1] Aphasie Coordination anormale[1] Vertiges[1] Paresthésie Tremblements[1] Trouble de l'équilibre[1] Trouble de mémoire[1] Dysphasie Dysarthrie Troubles de l'attention Troubles de la marche[1] Myoclonie	Hypokinésie
Affections oculaires	Des modifications de la pigmentation (décoloration) des tissus oculaires, incluant la rétine, ont été observées après plusieurs années de traitement. Certains de ces cas ont été associés à un trouble visuel	Diplopie Vision trouble	
Affections gastro-intestinales		Nausées Constipation Dyspepsie Sécheresse buccale	Dysphagie
Affections hépatobiliaires		Anomalies (augmentation) des tests fonctionnels hépatiques	
Affections de la peau et du tissu sous-cutané	Des décolorations bleu-gris des ongles, des lèvres et/ou de la peau ont été observées, généralement à des doses élevées et après plusieurs années de traitement		Rash cutané Hyperhidrose
Affections du rein et des voies urinaires		Dysurie Hésitation urinaire Hématurie Chromaturie	Rétention urinaire Néphrolithiase
Troubles généraux et anomalies au site d'administration	Fatigue	Asthénie Malaise Œdème périphérique	

(...)

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 – see Appendix V.

4.9 Overdose Symptoms and signs The data concerning overdose with retigabine are limited. 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 healthy 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. Treatment In the event of overdose, it is recommended that the patient is given appropriate symptomatic treatment as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be carried out as recommended by the national poisons centre, whenever possible.	**4.9 Overdose** Symptoms and signs The data concerning overdose with retigabine are limited. 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 healthy 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 symptomatic treatment as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be carried out as recommended by the national poisons centre, whenever possible. Haemodialysis has been shown to reduce the plasma concentrations of retigabine and NAMR by approximately 50%.
5.2 Pharmacokinetic properties (…) Metabolism Retigabine is extensively metabolised in humans. A substantial fraction of the retigabine dose is converted to inactive N-glucuronides. Retigabine is also metabolised to an N-acetyl metabolite (NAMR) that is also subsequently glucuronidated. NAMR has antiepileptic activity, but is less potent than retigabine in animal seizure models. (…) 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. No dose adjustment is recommended in patients with mild renal impairment (see section 4.2). In a single dose study in volunteers with end stage renal disease, the retigabine AUC was increased by approximately 100% relative to healthy volunteers. However, the effect of haemodialysis on retigabine clearance has not been sufficiently evaluated.	**5.2 Pharmacokinetic properties** (…) 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 much potent than retigabine in animal seizure models. 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. No dose adjustment 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 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.
6.3 Shelf life 18 Months	**6.3 Shelf life** 2 years

Appendix 2: European Risk Management Plan

Pharmacovigilance plan

This includes the following studies and analyses:

Prospective epidemiological study on urinary retention following TROBALT exposure, based on a US database of treated epileptic patients.

Pregnancy registries: North American (NAAED) and European (EURAP).

Study on a more flexible dose increase (in order to obtain optimal response and safety): study **RGB113905** which evaluated Trobalt immediate release as an adjuvant to monotherapies in adults with partial onset seizures treated by a flexible dosage regimen.

Study RTG116158 to evaluate the effects of retigabine added to existing antiepileptics on urinary function in patients with partial epielpsy.

Study RTG113284 to evaluate the pharmacokinetics and safety of retigabine in combination in subjects 12 to 18 years old with partial epilepsy or Lennox-Gastaut syndrome: suspended.

Study RTG113388 following the long-term safety of retigabine in the paediatric population (aged 12 or above) with partial epilepsy or Lennox-Gastaut syndrome : suspended.

European survey of patients and prescribers on their understanding of the risks associated with TROBALT (assessment of the prescriber's guide)

Minimisation activities

These include:

Routine activities: SPC, package leaflet, specific conditions for treatment initiation in order to reduce the risk for neuropsychiatric disorders and optimise compliance.

Additional risk minimisation activities with educational material. An information guide is designed for prescribers in order to educate them on the major risks to consider and discuss with their patients.

This guide includes the following messages:

- The need to follow a gradual dose increase at the start of treatment to minimise the risk of hallucinations, psychotic disorders and confusional state.
- The risk of inducing or potentiating urinary retention symptoms.
- The risk of lengthening the QT interval and the necessary caution in patients with heart disease or those taking concomitant medicines known to induce QT prolongation.
- The risk of occurrence of pigment change in ocular tissues, including the retina, and also the skin, lips and/or nails.
- The need for comprehensive ophthalmological examinations including visual acuity, slit-lamp examination, and dilated fundoscopy at treatment initiation and at least every 6 months thereafter while treatment is ongoing. If a change in retinal pigmentation or vision changes are detected, Trobalt should be discontinued unless no other appropriate treatment option is available.

Summary table of the risks and actions implemented in the European RMP

Risks		Actions implemented (in addition to routine pharmacovigilance)
Identified major risks	Voiding dysfunction and urinary retention	Targeted monitoring questionnaire for collecting adverse effects Assessment of urinary effects to optimise detection and better characterise the effects in current or future clinical studies RRMA: SPC sections 4.4, 4.8 and package leaflet PVP: Prospective epidemiological study on urinary retention ARMA: Educational material (prescriber's guide)
	Hallucinations, psychotic disorders and confusional state	Assessment of history (medical history and concomitant medicine) that could increase the risk of these effects Monitoring treatment discontinuations linked to hallucinations and psychotic disorders in planned and current clinical studies RRMA: Optimisation of the titration regimen with initiation boxes RRMA: SPC sections 4.4 and 4.8 and package leaflet, educational material (prescriber's guide) RMP PVP: Assess the rates of AEs and treatment discontinuations related to hallucinations and psychotic disorders in a study (RGB113905) on flexible dose increase (to determine whether a more flexible dose increase would improve safety)
	Weight gain	Monitoring weight gain in future clinical trials Assessment of the potential consequences of weight gain (e.g., metabolic syndrome, hypertension and heart disease) from post marketing data RRMA: SPC section 4.8 and package leaflet
	Pigment changes in ocular tissues, including the retina, and the skin, lips and/or nails.	Targeted monitoring questionnaire for collecting adverse effects. Continued analysis of the mechanism of action while referring patients from long-term studies presenting these type of effects for a dermatology consultation Ophthalmologic consultations for all patients from long-term studies VRX-RET-303 and 304 to see if these patients have ocular effects Letter to investigators (26/11/2012) DHPC (June 2013) RRMA: SPC sections 4.1 (restriction of indication), 4.4, 4.8 and leaflet ARMA: Educational material (prescriber guide)
Potential major risks	Effect on QT interval	Targeted monitoring questionnaire for collecting adverse effects linked to QT prolongation or torsades de pointes Enhanced monitoring of ECGs in future clinical studies on the use of retigabine in monotherapy Monitoring ECG changes when increasing doses in healthy volunteers in a study on the modified-release form (RTG113215) RRMA: SPC section 4.4 and package leaflet ARMA: Educational material (prescriber guide)
	Heart arrhythmias	Telemetry for 24 hours after a dose in healthy volunteers in a study of modified-release form (RTG113215 Cumulative review every 6 months of reports of cardiac arrhythmias to be included and analysed in the PSUR RRMA: SPC section 4.9 and package leaflet
	Accident risk secondary to neuropsychiatric effects	Monitoring reports of accidents/injuries in order to determine if there is a neuropsychiatric cause. Monitoring treatment discontinuations linked to adverse CNS effects in planned clinical studies RRMA: Optimisation of the titration regimen with initiation boxes RRMA: SPC sections 4.7, 4.8 and package leaflet RMP PVP: Study on a more flexible dose increase (RGB113905) to improve CNS safety.
	Increase in liver function tests	Targeted monitoring questionnaire for collecting adverse effects Additional monitoring of liver function tests in planned clinical studies Cumulative review every 6 months of reports of adverse effects linked to liver function RRMA: SPC section 4.8 and package leaflet

	Suicide risk	Targeted monitoring questionnaire for collecting adverse effects in clinical trials. Use of the Columbia scale in planned clinical studies RRMA: SPC section 4.4 and package leaflet
	Neutropenia	Serious and non-serious cases of neutrophil levels below $0.1x10^3$ should be reported to GSK within 24 hours More in-depth monitoring of severe infections that led to treatment discontinuation Assessment of haematological effects in order to determine potential risk factors
Missing Information	Use in pregnant or breastfeeding women	Pregnancy registries in the United States and Europe (EURAP and NAAED) RRMA: SPC section 4.6 and package leaflet
	Use in elderly	Active recruitment of patients above age 65 in planned clinical studies to evaluate the efficacy and safety of a modified formulation Assessment of study data in the indication postherpetic neuralgia including patients over age 65 PVP: Prospective epidemiological study on urinary retention including assessment of urine symptoms in the elderly Assessment of comorbidities associated with urinary retention such as benign prostatic hyperplasia In future phase III studies, sampling techniques used to monitor pharmacokinetic parameters for retigabine (assessment of the impact of covariables such as age on retigabine clearance) RRMA: SPC sections 4.2 and 4.4
	Use in adolescents and children	Paediatric studies conducted according to the paediatric investigation plan Monitoring of spontaneous notifications of off-label use RRMA: SPC section 4.2 and package leaflet
	Use in subjects with hepatic impairment	RRMA: SPC section 4.2 and package leaflet
	Use in subjects with renal impairment	RRMA: SPC section 4.2 and package leaflet
	Potential interaction with levetiracetam	RMP PVP: Study evaluating retigabine immediate-release in combination with each of the following monotherapies: carbamazepine/oxcarbazepine, lamotrigine, levetiracetam and valproic acid in adults with partial onset seizures treated by a flexible dosing regimen.

RRMA: Routine risk minimisation activities - ARMA: Additional risk minimisation activities - PVP Pharmacovigilance plan

Sections of the SPC 4.2: Dosage and method of administration; 4.4: Special warnings and precautions for use; 4.6: Pregnancy and lactation; 4.7: Effects on ability to drive and use machines; 4.8: Undesirable effects; 4.9: Overdose