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Committee for Medicinal Products for Human Use (CHMP)

Trobalt

(Retigabine)

Procedure No. EMEA/H/C/001245/II/0014

Marketing authorisation holder:
Glaxo Group Ltd

Variation Assessment Report

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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1. Scientific discussion

1.1. Introduction

Trobalt (retigabine) is an anti-epileptic drug (AED) being a neuronal potassium channel opener (KCNQ/Kv7). Retigabine was first authorised in the EU on 28th March 2011 and is available in Europe, the United States, Thailand and Chile.

Trobalt is indicated as adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.

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 clinical development programme for Retigabine includes the following long term studies:

- a number of long-term open-label extension (OLE) studies, two of which (VRX-RET-E22-303 and VRX-RET-E22-304) provide data in patients with up to six years of exposure to retigabine

- a Compassionate Use Programme (D-23129-3227), providing data in patients with more than 10 years of exposure to retigabine.

Adverse event reports of pigmentation/discolouration or co-incidental findings at study visits have been received from these long-running OLE studies and the Compassionate Use Programme. Most of these describe a blue-grey to purple discolouration of the nails and /or lips. A few reports also describe a blue/purple pigmentation of the skin and retinal pigmentation. The number of these cases reported to GSK has increased with time. This increase prompted a review by Global Clinical Safety and Pharmacovigilance (GCSP).

Adverse events relating to discolouration/pigmentation have only been observed in these above mentioned studies.

There are limited data on the nature of these events. However, while a number of measures were being taken in order to further characterise the nature of the events, the MAH submitted a variation update the label to describe these findings.

1.2. Clinical Safety aspects

1.2.1. Overview of safety data where discolouration events were detected

Clinical trials

- VRX- RET-E22-303; (RTG115098): A multicentre, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-301). A total of 181 patients were enrolled from centres in five countries in North and South America (Argentina, Brazil, Canada, Mexico, and United States). As of 5th September 2012, 42 subjects remain in the study.

- VRX-RET-E22-304; (RTG115097) A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302. A total of 375 patients were enrolled from countries in 13 countries from Europe, United States, Australia, Israel and South Africa. As of 5th September 2012, 64 subjects remain in the study.

These are ongoing open-label, long-term safety, tolerability, and efficacy studies of retigabine administered as adjunctive therapy. These studies were offered to patients who were expected to benefit from continued treatment with retigabine after successfully completing the maintenance and transition phase of the parent study (pivotal study VRX-RET-E22-301, which started in November 2005 and pivotal study VRX-RET-E22-302, which started in February 2006). A patient's dose of retigabine or other AEDs could be adjusted at investigator's discretion to optimise patient response and tolerability. Newly approved AEDs could be added and background AEDs discontinued, to achieve monotherapy with retigabine at investigator's discretion. Patients could remain in the study as long as their dose of retigabine remained in the range of 600 to 1200 mg/day.

Compassionate Use Programme (D-23129-3227)

This ongoing programme, which is being conducted under an open-label, long-term, named patient-treatment protocol, enrolled patients with refractory partial seizures who had derived significant benefit in Phase II OLE studies and were offered ongoing access to retigabine when the Wyeth-sponsored studies were discontinued in 2001. Patients could receive retigabine as an adjunct therapy to their ongoing AEDs, or were given the opportunity to take as monotherapy, at the discretion of the investigator. Information on SAEs, deaths and pregnancies are collected.
A total of 50 subjects enrolled in to the programme, from the United States, Europe, New Zealand, Australia and Israel. As of 5th September 2012, two subjects remain ongoing in the programme.

1.2.2. Signal of pigmentation/discolouration events

At the time of submission of this variation, an analysis with a cut-off date of 13th September 2012 revealed a total of 27 cases relating to pigmentation or discolouration following treatment with retigabine received from the long-term OLE studies 303 (n=14) and 304 (n=8) and the Compassionate Use programme (n=5). These events are summarised by the following information:

- 20 AEs of nail discolouration, 16 AEs of lip discolouration, 9 of skin discolouration and one of retinal pigmentation (diagnosed as *retinitis pigmentosa* by an ophthalmologist).
- The events presented after long-term exposure to retigabine with a median time to onset of 4.4 years (0.7 to 8 years.).
- There appears to be no trend with age or gender. The events tend to occur at higher doses (median dose where reported 1050 mg/day).
- In most cases, retigabine has been continued.
- Where specified, a causal relationship with retigabine was suspected.

However, few data was available at that time on which to evaluate these findings in terms of distribution, appearance, medical history, skin type, ethnic origin, sun exposure and whether the event(s) resolved on discontinuation of retigabine.

No spontaneous report of discolouration or pigmentation has been received.

The MAH initiated a number of investigations in the patients from these studies, as they have had the longest prolonged exposure to retigabine, in order to increase the chance of confirming the underlying features of the discolouration events.

The MAH informed investigators and patients participating in the on-going clinical trials of the discolouration events via updates to the Investigator Brochure and patient Informed Consent Forms. A Dear Investigator Letter (DIL) was issued to all active sites for studies VRX-RET-E22-303, VRX-RET-E22-304, and the treating physicians for two patients being treated under a Named Patient Program, to communicate the findings and to advise that patients with discolouration/pigmentation of the nails, lips and/or skin should be referred for a dermatology consultation. Consultation with an ophthalmologist for an ophthalmological examination was recommended for all patients remaining in studies VRX-RET-E22-303 and VRX-RET-E22-304 to investigate whether there are ocular effects in those patients receiving long-term treatment with retigabine.

These measures aimed to provide further detailed information on ongoing patients and where available, those who experienced discolouration events but who have discontinued from active clinical studies, to elucidate the possible underlying mechanism and better understand the cause for these events.

1.3. Other additional investigations

Non-clinical pharmacology / toxicology studies

Because the reports of pigmentation were associated with chronic dosing, the chronic dosing studies with retigabine were reviewed:

- 26 week oral (dietary) toxicity study in the rat D-23129/3000913454
- Two year oral (gavage) carcinogenicity study in the rat PR2005-080
- 13 week oral toxicity in the dog D-23129/3000896861
- 52 week oral toxicity study in the dog D-23129/3000912148

The review included the pathology reports, macroscopic and microscopic data from the studies along with any subsequent amendments (additional pathological investigations) for any incidences of pigmentation/discolouration.

With the exception of the 26-week oral study in rats there were no unusual or unexplained findings.

In the 26-week rat study a black globular pigment was observed microscopically, and was seen in association with lipofuscinosis of the intestine (particularly duodenum). This was an isolated finding in the gut, which was additionally not observed in the 2-year study. Therefore, the observed pigmentation was not considered to have any significance.

There were no corresponding macroscopic or microscopic changes (nonneoplastic or neoplastic) noted in the carcinogenicity study.
Levels of total labelled material (includes retigabine, metabolites and derivatives) in organs following a single dose of labelled retigabine indicate that no particular retention of radiolabel in any organ system examined was found.
The CHMP agreed that the preclinical programme does not provide suggestions of a mechanism for the findings. Non-clinical pharmacology/toxicology studies have shown that there was no recorded increased incidence of pigment in the potentially clinically-relevant tissues including skin, eye, and urinary bladder and because of the normal background incidence of pigmentation in intestine and kidney in the rodent, the clinical significance of these findings is unknown. In addition, tests showed that there was no particular retention of radiolabelled retigabine (retigabine and derivatives) in any organ system examined.
Supporting non-clinical investigations are currently being conducted including a re-evaluation of histopathology slides from previous retigabine non-clinical toxicology studies to assess for pigment accumulation in potentially clinically-relevant tissues including skin, eyes and urinary bladder. This may provide additional data to inform the clinical finding and/or the design of additional nonclinical investigations.

Urinalysis findings during the clinical development programme

During the clinical development programme, there were reports of purple crystals forming in urine samples and some reports of urine colouration (orange-brown). LC-MS/MS identified the crystals as retigabine (likely in the formation of dimers). The formation of retigabine solids are time dependent and seem to require both oxygen and light. It was speculated that the formation of these crystals are due to sample handling and processing and are unlikely to form *in vivo.* In addition retigabine has been shown to interfere with clinical laboratory assays of both serum and urine bilirubin, which can result in falsely elevated readings. The relevance of this finding to the reports of discolouration/pigmentation observed following long-term treatment is not known, but there is no evidence of tissue accumulation of retigabine from non-clinical studies.
Urinary crystals having the microscopic appearance of bilirubin have been described in urine samples collected during the Phase III trials (Studies 301, 302, 303 and 304). This involved 15% of patients (127 out of 843) and only occurred in patients who received active drug; there have been no reports in any of the other Phase I or Phase II retigabine studies. The crystals were not associated with any trends in clinical symptoms and no effects on relevant laboratory data or post-void residual urine volume (PVR) have been observed in these patients.
The MAH provided a comparison of clinical and biochemical profiles between patients who reported crystals and those who did not. In addition, a chemical analysis of urine samples containing crystals determined that the crystal were not bilirubin.

The CHMP acknowledged that there is no evidence of tissue accumulation of retigabine from non-clinical studies.
The MAH is currently attempting to chemically identify the purplish, water-insoluble crystalline drug substance observed in human urine samples through in vitro assessments. Understanding the origin

and identity of any coloured byproducts of retigabine formed in vitro, may help in the understanding and characterization of the discolouration observed in humans and in providing chemical identification in human biopsy samples.

Because there are no data on potential melanin binding of retigabine and/or metabolites of retigabine, GSK plans to investigate the potential for retigabine and/or retigabine-related materials (metabolites and/or degradants) to bind melanin in nonclinical assays. The design of these assays is currently in progress.

Published literature

It has been reported that drug-induced skin pigmentation accounts for 10-20% of all cases of acquired hyperpigmentation (Dereure 2001). Several drugs are implicated and there are a number of mechanisms of action reported, including (Dereure 2001):

- Drug or drug metabolite deposition in the dermis and epidermis
- Accumulation of melanin (overproduction or lack of clearance)
- Drug-induced post-inflammatory changes to skin
- Synthesis of pigments, such as lipofuscin

The clinical presentation of skin pigmentation varies according to the drug and the mechanism of action. The colour, appearance (patchy or diffuse) and location of the pigmentation appears to be extremely variable (skin, nails, lips etc). The rate of drug-induced pigmentation varies depending on the drug and cumulative dose. Patients with darker skin tend to be more affected as are those with greater sun exposure. There appear to be no differences in prevalence with age or between males and females.

1.3.1. Overall discussion

Discolouration/pigmentation of the nails, lips and skin

The Dear Investigator Letter (DIL) issued on 19th November 2012 to all investigators actively participating in VRX-RET-E22-303 and VRX-RET-E22-304 and the treating physicians of the two patients under the Named Patient Program, specified that patients with discolouration/pigmentation of the nails, skin and/or mucosal membranes should be referred for a dermatology consultation.

As part of this dermatology consultation, a Targeted Questionnaire was to be completed by the dermatologist conducting the consult to collect details which may provide further information on potential factors which may contribute to understanding potential mechanisms of action. This questionnaire was targeted at collecting relevant dermatological information in patients ongoing in Studies VRX-RET-E22-303 and VRX-RET-E22-304 who have presented with discolouration findings. It was anticipated that by following up patients with long-term exposure and with existing discolouration events, the underlying features of the discolouration events could be identified more expeditiously and may be used to provide information to update the retigabine label with any advisory statements, as

necessary. The questionnaire requests information on medical and medication history, ethnicity, time to onset of the event(s), whether retigabine was continued or discontinued and the outcomes arising from any actions taken (e.g. did the event resolve on stopping retigabine). The form also collects information on detailed description of the areas affected and how quickly the discolouration developed. The dermatologist is requested to provide copies of results and an interpretation of diagnostic tests, including results from nail clippings, biopsy, Woods lamp and photography. The Fitzpatrick Skin Scale is also provided to gather details on patients' genetic predisposition, sun exposure and skin type.

As of 2 May 2013, there have been 51 subjects with events relating to discolouration/pigmentation of nails, lips and/or skin (this includes the additional cases of discolouration of periocular tissue and eyelid discolouration found on eye exam and categorized as 'skin' discolouration) in the two long-term clinical studies and the compassionate use programme.

The events generally presented after long-term exposure to retigabine, with a median time to onset of 4.4 years (range 4 months to 6.9 years) (time to onset refers to date discolouration events were first reported; in some cases the patient is described as having the event(s) before mentioning them to the investigator).

There appeared to be no relation with age or gender.

Events tended to occur at higher doses, with the majority at 900 mg/day or higher (dose range between 600mg/day up to 1500mg/day). Note that the maximum approved dose of retigabine is 1200mg/day.

On review of the existing cases by a dermatologist, it is considered that the nail and skin discolouration/pigmentation is unlikely to be triggered by sun exposure, considering the anatomical location of the pigmentation (hard palate, toenails) and the fact that neither nail dystrophy nor photoonycholysis was observed.

To date, the biopsy reports available have been examined by a dermatologist at GSK. Based on these biopsy findings, it was considered that these cases are consistent with a non-immunological drug eruption that presents with discolouration/pigmentation.

The CHMP noted the currently available dechallenge information is limited. Some patients who had been found to have discolouration events have chosen to continue treatment. GSK will provide the CHMP with periodic updates of the events of discolouration, as information becomes available. The CHMP agreed with the plan to obtain further information presented by the MAH.

The CHMP agreed that the dermatological discolourations seem to be under appropriate evaluation with the detailed dermatological examination and reporting of this, together with the on-going toxicological re-investigations and the attempt to chemically identify the observed urine crystals.

However, the underlying mechanism for the findings is currently not understood.

Retinal pigmentation

The Dear Investigator Letter (DIL) issued on 19th November 2012 to all investigators actively participating in VRX-RET-E22-303 and VRX-RET-E22-304 and the treating physicians of the two patients under the Named Patient Program, specified that all active patients in these studies have a

consultation with an ophthalmologist for a comprehensive ophthalmological examination to investigate whether there are ocular effects in those patients receiving long-term treatment with retigabine.
An Eye Examination Worksheet was distributed with the DIL and included recommended ophthalmologic examinations, to include best corrected visual acuity testing, a comprehensive slit lamp examination and dilated funduscopic examination, with further ancillary testing (e.g. fundus photographs, formal visual fields, electroretinogram (ERG), electrooculogram (EOG), fluorescein angiography, etc) to be performed on the judgment of the examining ophthalmologist or by a retina specialist, based on the findings on the comprehensive eye examination.
These actions were described in the most recent EU RMP (Version 07, November 2012) as additional pharmacovigilance measures and were discussed in the most recent PSUR. In addition to the above measures, the following actions were also taken to ensure wider communication about these events:

- GSK initiated steps to change the product labelling in countries where the drug was approved, in order to reflect this adverse reaction to the nails, lips and skin.
- GSK has informed investigators and patients participating in the ongoing clinical trials of the discolouration events via updates to the Investigator Brochure and patient Informed Consent Forms.
- Information regarding these communications, and protocol amendments to studies VRX-RET-E22-303 and VRX-RET-E22-304, were submitted in countries with active subjects in these studies.

Since the variation application was submitted, the MAH is continuously gathering information on the ophthalmological consultations of the patients still participating in the ongoing trials mentioned before and the two patients in the compassionate program to further investigate the cases of retinal pigmentation and determine whether there is any impairment of visual field or impairment of retinal physiology which may predict future visual impairment.

Detailed patient narratives with information on the tests performed and the information awaited were provided through different updates.

As of 2 May 2013, GSK has received 56 cases of pigment changes to ocular tissues (including the retina) and of discolouration to the nails, lips and/or skin, 29 of which have been received from study VRX-RET-E22-303, 22 from study VRX-RET-E22304 and five from the Compassionate Use Programme.

As of 2 May 2013, there have been 55 eye exams received by GSK: Of the 55 subjects, there were 21 cases of pigment changes to ocular tissues, including 15 involving the retina.

From these 15 patients with retinal pigmentation, five patients had worse than 20/20 visual acuity. One of these patients had visual acuity of 20/160 in one eye, while the remaining four had visual acuity of 20/25 to 20/40 in one or both eyes. No baseline eye assessment is available for these patients.

Mild abnormalities on retinal electrophysiology tests have been reported in two further subjects. In one subject, an associated diagnosis of retinitis pigmentosa was made; and in this patient, a generalised reduction in the visual fields of both eyes on Humphrey Visual Testing was also noted. Visual acuity was reported to be normal in both subjects.

In the case diagnosed as retinitis pigmentosa, the pigment on the retina was first reported at approximately the same time as the discolouration events of the nails, lips and skin were observed. In this patient, follow–up ophthalmological evaluation more than one year after the initial consultation (and approximately one month after tapering off the drug was completed), demonstrated that the patient's presentation remained unchanged with respect to earlier examinations.

Although there is lack of information available on the time to onset of the ocular findings, the underlying mechanisms by which the ocular pigmentary effects occur are likely to be similar as those causing discolouration of the nails, lips and/or skin.

Even if it is unclear to what extent the pigment changes lead to visual impairment, the high proportion of patients affected was of great concern to the CHMP.

The MAH therefore proposed a restriction of the indication which will effectively make Trobalt last-line therapy in partial epilepsy.

The proposed restriction of the indication will read in the SmPC "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 drug combinations have proved inadequate or have not been tolerated".

This more refractory population carries a high risk of morbidity and mortality and will have already failed treatment with the more conventional AEDs utilising the more common Modes of Action.

In the registration trials, 25% of patients discontinued due to an AE, which were generally related to the central nervous system and were dose related. Most discontinuations occurred early in treatment during the titration phase and as such these patients would not be exposed to risk from the discolouration/pigmentation events that tend to be reported later during treatment. Therefore, even in this restricted population, it is highly likely that patients who have not received significant clinical benefit will discontinue retigabine before they are at risk of discolouration events occurring.

Events of retinal pigmentation have been reported in 15 patients in the phase 3 open-label extension studies and yet 12 have chosen to continue receiving treatment with retigabine under close monitoring. Of those who discontinued treatment, 2 did so for reasons of lack of efficacy, while one was reported to have discontinued due events of nail, lip and skin discolouration. At the present time data are limited from electrophysiological studies of the retina. In addition to the index case diagnosed with retinitis pigmentosa, only 1 other subject has completed their assessment with a retinal specialist. That subject was seizure free and retigabine has been continued. For all the other cases of possible retinal pigmentation, the results from ancillary testing are necessary for the principal investigator to assess the findings and to agree with the subject in determining the benefit versus the risk of continuing treatment.

A warning will be also introduced in section 4.4 of the Product Information recommending baseline and periodic comprehensive ophthalmological examinations (to include corrected visual acuity, dilated funduscopic exam via slit lamp exam) throughout treatment. Furthermore, retigabine should be discontinued if any retinal pigment or vision changes are observed, unless no other treatment options are available. If continued, the patient should be closely monitored and the potential risks assessed against the benefits of continuing treatment with retigabine.

The proposed ophthalmological examinations suggested by the MAH are considered sufficient to detect ocular abnormalities and identify any potential visual sequelae.

The CHMP recommended that ophthalmological examination should be carried out every 6 months since very limited information is available as to how fast the pigment changes progress.

A Dear Healthcare Provider (HCP) letter will be issued to communicate these recommendations.

1.4. Risk management plan

The MAH is requested to update the RMP expected with next PSUR in June 2013 in order to properly

reflect the restriction of the indication and the important safety concerns of pigmentation/discolouration.

1.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

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 drug combinations have proved inadequate or have not been tolerated. ~~Trobalt is indicated as adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.~~

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, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

4.8 Undesirable effects

System Organ Class	Very common	Common	Uncommon
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 .	
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

System Organ Class	Very common	Common	Uncommon

Changes were also made to the Package Leaflet in line with the above amendments.

In addition, as Trobalt was identified in the list of medicines undergoing additional monitoring, an inverted triangle will be included on the product information.

The symbol will allow patients and health care professionals to easily identify medicinal products that are undergoing additional monitoring, and its accompanying text will encourage them to report unexpected adverse reactions through national reporting systems.

The list of local representatives in the PL has also been revised.

1.6. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the restrictions for use of Trobalt and the pigment changes of ocular tissues, (including retina), skin, lips and nails.

The final version of this DHPC agreed by the CHMP is provided in Attachment 9 together with the communication plan.

2. Overall conclusion and impact on the benefit / risk balance

The benefit of retigabine as adjunctive treatment in partial epilepsy was established in the pivotal clinical trials submitted at the time of the initial Marketing Authorisation application.

Uncontrolled epilepsy carries a significant burden in terms of an increased risk of morbidity and mortality. Approximately 30% of patients remain uncontrolled despite treatment with other available AEDs, which have a number of different mechanisms of action. Retigabine with a novel mechanism of action offers treating physicians and their patients the opportunity to try a medicine, which acts differently to all other AEDs.

Now approximately two years since Trobalt was authorised, reports of discolouration and pigment changes in the skin, lips and nails, and pigmentation of ocular tissues, including the retina, begin to emerge. All reports originate from the long-term open-label extensions to the clinical trials forming the basis for the marketing authorisation (or an associated compassionate use programme). Almost all discolouration events occur after a minimum of two years retigabine treatment. This may explain why no post-marketing reports have drawn attention to the pigment changes since no or very few patients who started retigabine after marketing authorisation would have been treated long enough to develop the changes.

Even if the skin changes may be bothersome to patients, the pigmentation in the ocular tissues, especially in the retina, is considered to be the most important safety issue since they carry the potential to impair vision. So far there have been 21 cases of pigment changes (discolouration) of ocular tissue, including 15 involving the retina, after treatment with retigabine in two long-term clinical studies, and investigations continue as not all patients have examined yet. This is a very high proportion of patients, and even if baseline information is very sparse, it suggests that retinal pigmentation is indeed a very common undesirable effect of long-term treatment with retigabine.

Some of these 15 patients have impaired vision whereas others have normal vision as measured by visual acuity. It is very difficult to judge if the cases of visual impairment are caused by the retinal

pigmentation or if they are caused by pre-existing co-morbid conditions. Unfortunately, baseline information about vision and pre-disposing factors is very limited. It should be noted that the patients represent a chronic epilepsy population which cannot be satisfactorily treated with mono-therapy, and it is not unlikely that they could be pre-disposed to visual impairment compared to a non-epilepsy population. Further, there appear not be to be very strong correlation between the extent of the pigment changes and the reported visual impairment.

On the other hand, at this stage it cannot with any reasonable certainty be excluded that retinal pigmentation induced by retigabine treatment has caused or contributed to the reported cases of impairment of visual acuity or reduction of visual field – or will do so in the longer term.

It is noteworthy that the vast majority of patients with identified retinal pigmentation (12 out of 15) continued retigabine therapy despite the observation of the findings. This suggests that the physicians in charge of the treatment saw no viable treatment alternative for these patients. In the remaining patients who did discontinue treatment, only one patient appeared to do so because of the pigment changes. Also considering that retigabine represents a new mode of action, this speaks in favour of a benefit in some, very difficult-to-treat patients with partial epilepsy.

Overall, it is considered likely that some treatment-resistant patients obtain satisfactory seizure control with retigabine and that these patients cannot be treated satisfactorily with other anti-epileptic medicines.

Benefit-risk balance

As highlighted above, the retinal pigment changes are very important as they could potentially result in severe visual impairment or even blindness. At present the nature, possible mechanism and natural history of these events still needs to be elucidated. However, due to the potential risks the indication of Trobalt has been restricted as last-line therapy in partial epilepsy.

In addition, Health Care Professionals should request a comprehensive ophthalmological examination (including visual acuity, slit-lamp examination, and dilated fundoscopy) performed at baseline and every six 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. Also in patients who develop discolouration of the nails, lips or skin, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

With the proposed restricted indication and the recommendations for monitoring, only treatment-resistant patient with no other treatment options should be treated with retigabine, and patients should have an ophthalmological examination before treatment and at least every six months during treatment. These measures are considered adequate to ensure that only the most treatment-resistant patients will be treated and that the treating physician will be monitoring patients for retinal pigmentation or deterioration in vision, and prompted to perform a thorough, individual benefit-risk assessment at treatment start and when retinal pigment changes arise during treatment.

Therefore, with the above mentioned risk minimisation measures, the planned investigations and follow-up actions to further understand the concern, the benefit-risk balance for retigabine in this restricted population is considered positive.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and

therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of section 4.1 of the SmPC to restrict the indication to 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. In addition, warnings of pigment changes (discolouration) of ocular including the retina, lips, skin and nails have been introduced in section 4.4 and 4.8 of the SmPC with recommendations for ophthalmological examinations before and during treatment.

The Package Leaflet has been amended accordingly.

In addition, the key messages of the physician's guide have been updated in Annex II and as Trobalt was identified in the list of medicines undergoing additional monitoring, the inverted triangle will be included on the product information.

The MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **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 all physicians who are expected to prescribe TROBALT are provided with a physician information pack containing the following elements:

- The Summary of Product Characteristics
- A physician's guide to prescribing including 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;
    - 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 retinal pigment or vision changes are detected, TROBALT should be discontinued unless no other suitable treatment options are available.

4. EPAR changes

The EPAR module 8 "*Steps after the authorisation*" will be updated as follows:

Scope

Update of section 4.1 of the SmPC to restrict the indication to 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. In addition, warnings of pigment changes (discolouration) of ocular including the retina, lips, skin and nails have been introduced in section 4.4 and 4.8 of the SmPC with recommendations for ophthalmological examinations before and during treatment.

The Package Leaflet has been amended accordingly.

In addition, the key messages of the physician's guide have been updated in Annex II and as Trobalt was identified in the list of medicines undergoing additional monitoring, the inverted triangle will be included on the product information.