26 July 2018
EMA/549064/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kigabeq

International non-proprietary name: vigabatrin

Procedure No. EMEA/H/C/004534/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse event(s)
AEDs	Antiepileptic drugs
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
ASMF	Active Substance Master File = Drug Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under plasma concentration-time curves
BCS	Biopharmaceutics Classification System
C/D	concentration to dosage ratio
CBZ	carbamazepine
CEP	Certificate of Suitability of the EP
CI	Confidence interval
CNS	Central nervous system
CPS	Complex Partial Seizures
CSF	Cerebrospinal fluid
CSS	Steady-state plasma concentrations
DSC	Differential Scanning Calorimetry
EC	European Commission
EEG	Electroencephalograph/y
ERG	Electroretinogram
GABA	Gamma-aminobutyric acid
GABAT	Gamma-aminobutyric acid transaminase
GC	Gas Chromatography
GCP	Good clinical practice
GI	gastrointestinal
HC	Hydrocortisone
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICISS	International Collaborative Infantile Spasms Study
IR	Infrared
IS	Infantile spasms
ITT	Intention to treat
IU	International Unit
KF	Karl Fischer titration
LTG	Lamotrigine
MAA	Marketing Authorisation Application
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
NMR	Nuclear Magnetic Resonance
OR	Odds ratio
PDCO	Paediatric Commitee
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric investigation plan
pKa	Negative Log of Ka
POS	partial onset seizures
PP	Per protocol
PP	Polypropylene
pVFDs	Peripheral visual field defects
QbD	Quality by design
QTPP	Quality target product profile
rCPS	Refractory complex partial seizures
RH	Relative Humidity
rpm	Rate Per Minute
RSD	Relative standard deviation
SAE	Serious adverse event(s)
SmPC	Summary of Product Characteristics
TSC	Tuberous sclerosis
UKISS	United Kingdom Infantile Spasms Study
UV	ultraviolet
V	Visit(s)

VABAM	VGB-associated brain abnormalities
VABS	Vineland Adaptive Behaviour Scales
VAVFL	VGB-associated visual field loss
VEPs	Visual-evoked potentials
VFDs	Visual field defects
VFL	Visual field loss
VGB	Vigabatrin
VGBRD	VGB-induced retinal damage
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ORPHELIA Pharma SAS submitted on 29 May 2017 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for KIGABEQ, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2016.

The applicant applied for the following indication:

KIGABEQ is indicated in infants and children from 1 month to less than 7 years of age for:

- Treatment in monotherapy of infantile spasms (West's syndrome).

- Treatment in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product SABRIL 500 mg Granules for oral solution in sachet and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: SABRIL 500 mg Granules for oral solution in sachet
- Marketing authorisation holder: SANOFI AVENTIS
- Date of authorisation: 22 March 1993
- Marketing authorisation granted by:
  - Member State (EEA) : France
- Marketing authorisation number: 337 806-4

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: SABRIL 500 mg Granules for oral solution in sachet
- Marketing authorisation holder: SANOFI AVENTIS
- Date of authorisation: 22 March 1993
- Marketing authorisation granted by:
  - Member State (EEA): France
- Marketing authorisation number: 337 806-4

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: SABRIL 500 mg Granules for oral solution in sachet
- Marketing authorisation holder: SANOFI AVENTIS
- Date of authorisation: 22 March 1993

- Marketing authorisation granted by:
  - Member State (EEA): France
  - Marketing authorisation number(s): 337 806-4
- Bioavailability study number(s): 2014-000360-17

Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0083/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0083/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0083/2017.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	29 May 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	1 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	15 November 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 February 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 April 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 April 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 April 2018

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	25 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 June 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 June 2018
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	5 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to KIGABEQ on	26 July 2018

2. Scientific discussion

2.1. Introduction

Kigabeq 100 mg and 500 mg are scored soluble tablets containing 100 or 500 mg vigabatrin as drug substance. Vigabatrin (VGB) is an amino-acid derivative and a close structural analogue of gammaaminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. Vigabatrin is made as a racemic mixture of its two enantiomers, only the S(+) enantiomer being pharmacologically active. Vigabatrin irreversibly inhibits γ-aminobutyric acid transaminase (GABA-T), the GABA degrading enzyme, whereby it increases GABA levels in the central nervous system. Thereby, vigabatrin leads to a reduction in seizure activity in patients suffering from resistant partial epilepsy or infantile spasms (IS).

Vigabatrin was first licensed as an antiepileptic agent in the UK and the Republic of Ireland in 1989 (Sabril, Sanofi Aventis). By the late 1990s, it had been accepted into mainstream clinical practice in the care of adult and pediatric patients in over 40 countries. Vigabatrin was the first therapeutic agent to be approved by the Food and Drug Administration (FDA) for the treatment of infantile spasms (IS) as monotherapy, as well as for adjunctive use in the treatment of resistant focal epilepsy. It represents an important progress for patients who present forms of epilepsy which are difficult to manage.

Currently marketed formulations of vigabatrin (Sabril) are only available as 500 mg film-coated tablets and 500 mg granules for oral solution sachets. These formulations may prove to be cumbersome to administer especially in paediatric patients aged from 1 month to below 7 years suffering from resistant partial epilepsy, for whom often manual splitting of the sachet or lengthy and error-prone dilutions are required. Therefore, a medical need for an age appropriate formulation was recognized and acknowledged by the Paediatric Working Party in the Assessment of the paediatric needs - Epilepsy (EMEA/377174/2006) and by PDCO Draft inventory of paediatric therapeutic needs - Neurology ((EMA/562919/2013).

Therefore, Kigabeq 100 mg and 500 mg scored soluble tablets were developed by ORPHELIA Pharma, France, to allow better dose adjustments to body weights (incremental unitary dose of 50 mg) and to limit wastage of unused drug in paediatric patients from 1 month to less than 7 years. The product is indicated for infants and children in the named age class for treatment of IS as monotherapy and for use in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy with or

without secondary generalisation in which other appropriate medicinal product combinations have proved inadequate or have not been tolerated. Kigabeq 100 mg and 500 mg soluble tablets can also be administered via nasogastric tube.

2.1.1. Disease or condition

Kigabeq is indicated in infants and children from 1 month to less than 7 years of age for:

- Treatment in monotherapy of infantile spasms (West's syndrome).
- Treatment in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy (focal onset seizures) with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated.

2.1.2. Epidemiology

West syndrome is a unique and severe form of epilepsy occurring in infants which is associated with a specific and highly resistant seizure type (Infantile spasms (IS)), a specific electro-encephalographic pattern (hypsarrhythmia), and a rapid psychomotor regression. Infantile spasms (IS) constitute 2% of childhood epilepsies in the US but 25% of epilepsy with onset in the first year of life. The rate of infantile spasm is estimated to be 2.5-6.0 cases per 10,000 live births. Its prevalence rate is 1.5-2.0 cases per 10,000 children aged 10 years or younger. Infantile spasm occurs in 0.05 (Estonia) to 0.41 (Oulu, Finland) of 1000 live births and in 1.4% (Estonia), 4.2% (Odense, Denmark), and 7.6% (Tampere, Finland) of children with epilepsy.

2.1.3. Aetiology and pathogenesis

Infantile spasms are believed to reflect abnormal interactions between the cortex and brainstem structures. Focal lesions early in life may secondarily affect other sites in the brain, and hypsarrhythmia may represent this abnormal activity arising from multiple brain sites. The frequent onset of infantile spasms in infancy suggests that an immature central nervous system (CNS) may be important in the syndrome’s pathogenesis.

2.1.4. Clinical presentation, diagnosis and prognosis

A large panel of aetiologies may result in IS (malformative, anoxo-ischemic or infectious brain lesions, metabolic or genetic diseases). Other seizure types and neurological features may be present from early phase depending on the aetiology. IS are frequently associated with poor neurologic and developmental long-term outcomes including psychomotor delay, development of other seizure types, impaired cognitive and psychosocial functioning, and mortality in a small but significant number of patients. Because continued spasms and abnormal electroencephalograph (EEG) patterns associated with IS proved to have detrimental impact on long-term development, rapid and complete control of spasms is the primary goal of treatment (O’Callaghan et al, 2011). For this reason cessation of spasms was the primary endpoint for documenting vigabatrin efficacy.

2.1.5. Management

Hormonal therapies, including adrenocorticotropic hormone (ACTH) and corticosteroids, and vigabatrin have the most evidence to support their use in infantile spasms. Many other treatment options continue

to be explored, including the ketogenic diet, traditional anti-epileptic medications, and resective surgery in select cases.

ORPHELIA Pharma SAS has developed a new pharmaceutical form for vigabatrin as scored soluble tablets of 100 mg and 500 mg strength. The proposed soluble tablets are to be used as oral solution for infants and children below 7 years and are bioequivalent to the reference product “Sabril 500 mg granulés pour solution buvable”. In addition, Kigabeq 100 mg and 500 mg soluble tablets can be administered via nasogastric tube.

The new pharmaceutical form allows to better adjust the dose to body weight (incremental unitary dose of 50 mg) and to limit wastage of unused drug. The currently marketed vigabatrin (Sabril) form only exists as 500 mg film-coated tablets (for adults and children above 6 years) and 500 mg granules for oral solution sachets. Sabril is not adapted for administration to infants or when a fraction of the sachet is needed. Manual splitting of the sachet or lengthy and error-prone dilutions are often required. The new formulation of vigabatrin developed by the applicant is therefore considered to meet a medical need in the paediatric population. Compared to the reference product the possibility of nasogastric tube administration constitutes an additional benefit for small and/or severely sick children who are unable to swallow.

2.2. About the product

The Applicant submitted a hybrid application for paediatric use marketing authorisation (PUMA) of Kigabeq 100 mg and 500 mg soluble tablets with respect to the reference product "Sabril 500 mg granulés pour solution buvable en sachet-dose" (Sanofi Aventis), which has been marketed since 1993 in France. Due to the additional dose strength (100 mg tablet), the divisibility of Kigabeq soluble tablets and the additional proposed route of administration via nasogastric tubes the proposed products do not fall within the strict definition of a ‘generic medicinal product’ and thus an application in accordance with Article 10(3) of Directive 2001/83/EC ("hybrid") was considered appropriate.

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

The need for developing an age-appropriate formulation of vigabatrin for the treatment of IS and resistant partial epilepsy has been confirmed successively in the 2 following documents published by the EMA:

- ✓ “Assessment of the paediatric needs-epilepsy”- 20 September 2006 (EMEA/377174/2006) agreed by Paediatric Working Party (PEG) in November 2005;
- ✓ “Inventory of paediatric therapeutic needs - neurology” – 15 November 2013 (EMA/562919/2013) agreed by PDCO in October 2013.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as scored soluble tablets containing 100 or 500 mg of vigabatrin as active substance.

Other ingredients are: crospovidone type B, mannitol and sodium stearyl fumarate.

The product is available in HDPE bottle closed with a child resistant tamper evident PP screw cap as described in section 6.5 of the SmPC.

2.4.2. Active substance

General information

The chemical name of vigabatrin is (4*RS*)-4-aminohex-5-enoic acid corresponding to the molecular formula $C_6H_{11}NO_2$. It has a molecular mass of 192.2 g/mol and the following structure:

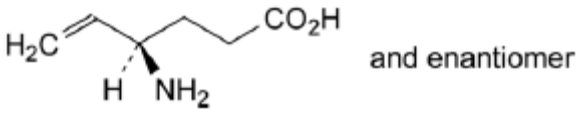


Figure 1: Vigabatrin structure

The chemical structure of vigabatrin was confirmed by a combination of ^{1}H and ^{13}C NMR spectroscopy, XRPD diffraction, IR spectroscopy, DSC, mass spectrometry and elemental analysis.

The active substance is a white or almost white powder. It is freely soluble in water, slightly soluble in methanol and practically insoluble in methylene chloride. The active substance is slightly hygroscopic in nature when exposed to 25 °C / 80% RH for 24 hours.

Vigabatrin exhibits stereoisomerism due to the presence of a chiral centre. Vigabatrin has been supplied as racemic compound, as per Ph. Eur. standards.

Based on literature vigabatrin exhibits two different polymorphs; form I, which is thermodynamically stable form, and another one is metastable form, which will convert to form I under ambient storage conditions over a period of months. Both forms can be distinguished through IR testing.

As there is a monograph of vigabatrin in the European Pharmacopoeia, one of the manufacturers of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application (MAA).

Manufacture, characterisation and process controls

Two suppliers of the active substance are proposed and both CEP and Active Substance Master File procedures have been used within the MAA.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance supported by the ASMF is synthesized in three main steps with two isolated intermediates, using a commercially available well-defined starting material with acceptable specification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting material and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, solubility (Ph. Eur.), identification (IR), water content (KF), sulfated ash (Ph. Eur.), related substances (HPLC), assay (Ph. Eur., HPLC for shelf-life) and residual solvents (GC).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents. All additional methods have been adequately validated and described according to ICH Q2.

Stability

Stability data from six commercial scale for the first and four commercial scale batches of the active substance from the second proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 ºC / 60% RH) for the manufacturer supported by the CEP and for up to 60 months under intermediate conditions (30 ºC / 65% RH) for the manufacturer supported by the ASMF were provided. Up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided by both manufacturers for these batches.

The following parameters were tested: appearance, water content, related substances and assay (HPLC).

Photostability testing following the ICH guideline Q1B was performed on one batch by the ASMF Holder. No changes in the quality of the active substance were observed, demonstrating that the active substance is stable. Results on stress conditions: temperature, effect of oxidation, effect of photolysis and effect of hydrolysis (at both acidic and basic pH) were also provided on one batch. The analytical methods used were the same as for release except the HPLC method for impurities which is used for shelf-life testing only, and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period with no special storage conditions in the proposed container.

2.4.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as scored soluble tablet formulations of two strengths containing 100 mg or 500 mg of vigabatrin as the active substance.

Kigabeq soluble tablets are white oblong tablets with a score-line on one side. The score line allows adjusting the dosing strength by breaking the tablet in two equal parts to comply with the posology. The suitability of the score line was adequately demonstrated.

The two strengths differ by size: dimensions of the 100 mg tablets are 9.4 mm x 5.3 mm and the dimensions of the 500 mg tablets are 16.0 mm x 9.0 mm.

The aim of pharmaceutical development was to develop an age-appropriate formulation of vigabatrin to be used in the treatment of infantile spasms (IS) and resistant partial epilepsy which would simplify the administration of the product compared to the product already on the market. A soluble tablet was chosen as a pharmaceutical form as it combines the advantages of a solid dosage form (better stability over a long period of time, no need of preservatives) and the ease of administration of a solution.

Pharmaceutical development of the finished product contains QbD elements; however no design space has been claimed.

The quality target product profile (QTPP) was defined as solid dosage form with fast disintegration time of less than 3 minutes at 37 ºC and if possible below 1 minute at 15-25 ºC; a dosage form should be of highest possible active substance loading; it should contain 100 mg or 500 mg of active substance formulated with children-friendly excipients in scored tablets to allow for adjustment of the dose given to the patient.

The solubility of vigabatrin in aqueous solution is very high, independent of the pH. Based on performed solubility studies, vigabatrin was classified as a BCS class I substance.

Since vigabatrin exhibits a high solubility, the particle size will likely have no impact on the kinetics of dissolution.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The active substance compatibility with the excipients has been demonstrated by stability data generated in accelerated and long-term stability studies on the finished product.

Mannitol is not present in the reference medicinal product Sabril, and as it may affect gastrointestinal transit, the CHMP requested a further substantiation of claimed bioequivalence between the reference medicinal product and Kigabeq tablets. A bioequivalence study was performed between Kigabeq 500 mg soluble tablets and the reference product Sabril 500 mg, granules for oral solution to generate evidence that Kigabeq 500 mg soluble and the reference product have a bioequivalent pharmacokinetic profile.. Justification for requesting bio-waiver for the lower strength i.e. Kigabeq 100 mg soluble tablets is prepared according to general bio-waiver criteria as specified in the Guideline on the Investigation of Bioequivalence. Kigabeq 100 mg satisfy the conditions for bio-waiver of *in vivo* bioequivalence study with Kigabeq 500 mg soluble tablets (both strengths are manufactured by the same manufacturing process, the qualitative composition of both strengths is the same, both strengths show a quantitatively proportional composition and both strengths show appropriately similar *in vitro* dissolution characteristics).

Fast disintegration is an essential characteristic of a soluble tablet. Hence disintegration studies were conducted during pharmaceutical development. The disintegration and dissolution studies under clinical practice conditions show that Kigabeq 100 mg and 500 mg soluble tablets disintegrate quickly in small volumes of water (less than 1 minute under Ph. Eur. conditions and less than 30 seconds under clinical practice conditions) and the active substance, as expected since it is freely soluble in water readily dissolves (more than 85% of the labelled amount is dissolved within 3 minutes in all three buffer media,

pH 1.2, 4.5 and 6.8 under Ph. Eur. conditions, and more than 90% of the labelled amount is dissolved after 60 seconds under clinical practice conditions).

Kinetics of dissolution of both strengths of the finished product was tested by an *in vitro* dissolution in different media in comparison to the reference medicinal product "Sabril 500 mg, granulés pour solution buvable en sachet-dose". Additionally, the dissolution performance of Sabril 500 mg film coated tablets was investigated for information. The study was carried out in accordance with Appendix III of the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and dissolution profiles were established within the physiologically relevant pH range of pH 1 – 6.8, namely at pH 1.2, 4.5 and 6.8. Consistently, Kigabeq soluble tablets 100 mg and 500 mg and the reference product Sabril 500 mg granulates in sachets show "very rapid" dissolution properties in all buffer media, pH 1.2, 4.5 and 6.8 since more than 85% of the labelled amount is dissolved within 3 minutes. Therefore, similarity of dissolution profiles between test and reference product is demonstrated according to Appendix I of the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and further mathematical evaluations are not needed. This study shows that even if Kigabeq soluble tablets 100 mg and 500 mg and Sabril™ 500 mg granulates in sachets were taken as a solid form, their dissolution profiles are considered similar. In fact, in clinical practice conditions, they are administered to the patients as solutions.

Kigabeq 100 mg and 500 mg soluble tablets are intended to be dissolved in water and administered to the patient as a solution. Thus, stability of the active substance in the reconstituted liquid is of importance in clinical practice and stability of the finished product in solution obtained after dissolution of the soluble tablets in tap water under normal conditions (25 °C) has been established. The finished product dissolved in tap water is stable for 1 hour at 25 °C.

The primary packaging is HDPE bottle closed with a child resistant tamper evident PP screw cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Compatibility (including dose recovery) of Kigabeq soluble tablets with nasogastric tubes, syringes and cups (different plastic devices used for drug administration in clinical practice) has been assessed in a study. The results of the study indicate that there is no adsorption of vigabatrin on nasogastric tubes made of polyurethane or silicone. Moreover, the results further demonstrate that vigabatrin is not adsorbed neither on polypropylene commonly used in the course of preparation of the reconstituted liquid (cup) nor in the course of administration (syringe).

Manufacture of the product and process controls

The manufacturing process consists of the following steps:

- Blending
- Granulation
- Tabletting
- Packaging

Major steps of the manufacturing process have been validated by a number of studies on 3 pilot scale batches of both tablet strengths. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of tablets, appearance of solution, identification (HPLC, IR), disintegration (Ph. Eur.), pH of solution (Ph. Eur.), average mass (Ph. Eur.), uniformity of dosage units by mass variation (Ph. Eur.), assay (HPLC), related substances (HPLC) and microbiological purity (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 pilot scale and 1 sub-pilot scale batches of each strength of the finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 18 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Batches using the active substance from both suppliers were investigated and showed no difference in stability.

Samples were tested for appearance of tablets, appearance of solution, disintegration, pH of solution, average mass, assay, related substances and microbiological purity. The analytical procedures used are stability indicating.

No significant changes have been observed

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the photostability study show that there is no evidence of degradation of the finished product when exposed to light.

In-use stability data on one clinical batch per strength are presented covering 30 days of in-use period. It was performed on two clinical batches simulating daily withdrawal of tablets. A second in-use stability study was initiated on one primary batch of each strength covering 100 days. No significant differences for any of the parameters could be observed in the in-use stability study after 30 days of daily opening of the HDPE bottle. All results obtained in the second in-use stability study showed no significant changes for all parameters tested over a period of 100 days. Compliance with the acceptance criteria of the shelf-life specification for the maximum duration of use demonstrates the appropriate in-use stability of the finished product.

Based on available stability data, the proposed shelf-life of 30 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable. The product should be used immediately following preparation of the oral solution.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the assessment, the results of a bioequivalence study between the finished product and the reference medicinal product were presented in order to substantiate the bioequivalence, at the request of CHMP.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the the finished product.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.5.2. Pharmacology

Vigabatrin is an amino-acid derivative which irreversibly inhibits gamma-aminobutyric acid transaminase (GABAT), the GABA degrading enzyme, thus increasing GABA in the central nervous system (CNS). This increased level of GABA leads to a reduction in seizure activity. Pharmacodynamic properties of the drug are correlated to the rate of de-novo synthesis of the GABA-T enzyme, and not correlated to plasma concentration of the drug. In addition, some evidence suggests that vigabatrin may inhibit glial uptake of GABA and may also stimulate GABA release. As GABA is the major inhibitory neurotransmitter in the CNS of mammalian brain, a deficiency in the GABAergic system has been demonstrated to be associated with certain forms of epilepsy.

Vigabatrin has been shown to cause a dose-dependent, permanent peripheral field constriction. The clinical recognition of a peripheral visual field defects (pVFDs) in certain patients prescribed vigabatrin has led to closer assessment of retinal toxicity in various animal models. In albino rats, vigabatrin was demonstrated to be retino-toxic. Retinal lesions were observed in 80 to 100% of the animals at an oral

dose of 300 mg/kg/day and were not observed in the pigmented rat, the dog or the monkey (EMEA - CPMP/1357/99). It is suggested that the visual field loss in vigabatrin -treated epileptic patients may result from a severe disorganization of the photoreceptor layer. The incidence and severity of the lesions is reasonably dose-related. The dose-related morphological and electrophysiological changes indicated a retinal pathology that may explain the constricted visual fields seen in some patients treated with vigabatrin.

The vigabatrin use may also be the cause of some neurological effects. The only consistent histopathologic finding in rats and dogs was microvacuolation of specific regions of the brain, predominantly within the white matter termed Intramyelinic Oedema (IME). IME has not been seen in the spinal cord or peripheral nerves of any species. The mechanism of damage could be direct toxicity of vigabatrin or an indirect effect mediated through elevated GABA levels.

During the procedure, at the CHMP's request the Applicant revised and updated the nonclinical overview and presented studies conducted in immature animals, while stressed that the vigabatrin as active pharmaceutical ingredient is already used for decades in the proposed indications in children and infants. Considering the legal basis of this application as a hybrid application and the well-known safety and efficacy profile of vigabatrin in the paediatric population, the CHMP is of the opinion that the absence of further pre-clinical studies in pre-mature animals is considered acceptable.

2.5.3. Pharmacokinetics

No new nonclinical pharmacokinetic studies have been performed for this application. Given the nature of the application the CHMP considers this acceptable.

The pharmacokinetics and metabolism of vigabatrin following oral administration have been well described. Vigabatrin absorption is dose-dependent and may be described by Michaelis-Menten type absorption. Below 30 mg/kg the absorption rate and extent was apparently independent of the vigabatrin dose, indicating non-saturated absorption. However, at an oral dose of 300 mg/kg the bioavailability of vigabatrinwas lower indicating a saturable absorption mechanism.

Vigabatrin does not bind to plasma proteins and as a highly water-soluble compound it distributes widely in the body. The radiolabelled drug was demonstrated to be widely distributed throughout the body. In vitro studies on the passage of vigabatrin across the human placenta demonstrated that the transfer from maternal to foetal blood is low and comparable to that of other α-amino acids. No primary sources on the metabolism of vigabatrin in animals were identified. In humans vigabatrin is not significantly metabolised.

Elimination of vigabatrin from serum in rats administered various single doses by i.p. injection was shown to be rapid with mean t1/2 values of 1.1 – 1.4 hours and independent from the dose. In humans, approximately 80% of the dose is eliminated unchanged in the urine within 24 hours, with less than 5% of the dose accounting for by metabolites.

2.5.4. Toxicology

No new toxicity studies have been performed for this application and as an Article 10(3) Hybrid Application under Directive 2010/83/EC this is considered acceptable by the CHMP.

Vigabatrin has a relatively low degree of acute toxicity in several animal species. The oral median lethal dose in rodents was approximately 3,000 mg/kg. The available single dose toxicity data suggest an adequate safety margin for vigabatrin when used according to the restrictions specified in the SmPC.

The GABA-transaminase inhibitor, vigabatrin, has been shown to have a rather low degree of acute toxicity in several animal species. Oral administration of the drug at 1,000 mg/kg/day for 2-4 weeks caused decreased food consumption and weight loss with resultant prostration and death in both rats and dogs. Dosages of 200 mg/kg/day were tolerated for a year without clinical signs in dogs, although rats suffered reduced weight gains and convulsions after 3-4 months when given the drug in the diet. The convulsions continued to occur frequently throughout the one-year study, but abated 3-4 months after cessation of treatment. The only consistent histopathologic evidence of toxicity in rats and dogs has been the finding of intramyelinic edema (microvacuolation) in the brain, most notably in certain areas of white matter (cerebellum, reticular formation and optic tract in rats and columns of fornix and optic tract in dogs). No lesions were found in the spinal cord or peripheral nervous system. It took several weeks for the microvacuolation to develop, even at high dosages, but it did not continue to progress thereafter, even though a slight effect was noted at dosages as low disappeared within a few weeks after treatment was withdrawn. No residual effects were observed in dogs, whereas rats exhibited swollen axons and microscopic mineralized bodies in the cerebellum. Monkeys exhibited no adverse clinical effects except for occasional loose stools at 300 mg/kg/day.

Vigabatrin was shown not to be genotoxic. In standard mutagenicity studies, vigabatrin did not induce gene mutations or chromosomal damage. Vigabatrin was shown not to be carcinogenic (Ovation, 2008). Carcinogenicity studies indicate that vigabatrin is not a potential carcinogen nor did it adversely affect life expectancy in the two species studied (rat and mouse).

Vigabatrin did not augment the spontaneous incidence of neural tube defects characteristic of this strain, but accelerated destruction of the brain in spontaneous exencephalic embryos. Mandibular and maxillary hypoplasia, arched palate, cleft palate (two cases), limb defects (one case), and exomphalos were observed in the malformed foetuses. The high incidence of exomphalos appears to be a unique result of vigabatrin treatment. In view of the paucity of human and animal data on the reproductive toxicologic effects of vigabatrin, the results of the presented study assumed particular importance and suggested that vigabatrin should be used in pregnancy with extreme caution (Abdulrazzaq et al., 1997). This information is adequately stated in the proposed SmPC. Moreover, the proposed product is not intended for the use in women of child-bearing age and the safety profile of the use of vigabatrin in the paediatric population is well-known from the reference product.

2.5.5. Ecotoxicity / environmental risk assessment

The applicant submitted environmental risk assessment (dated 01 September 2016) for the medicinal products Kigabeq, 100 mg/500 mg soluble tablets, containing 100 mg or 500 mg Vigabatrin as the active substance which has been written according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/HMP/SWP/4447/00 corr 2*, 01 June 2006).

The applicant presented the rationale for the absence of ERA studies conducted for this application.

An analysis of market data for 6 years (2010 - 2015) revealed that the consumption of drug products containing Vigabatrin as drug substance decreased during the period 2010 - 2015.

Vigabatrin is characterised by a low toxicity, good water solubility and very low Water-Octanol-Partition Coefficient. The analysis of the market data revealed a decrease of the Vigabatrin consumption in Europe during the last 6 years. Due to the improved dosage options for infants wasting of drug substance will be largely prevented. Accordingly, no increase of released amounts of Vigabatrin in the following years has to be expected. Authorized products containing vigabatrin as drug substance are marketed under the trade name Sabril or Sabrilex in 23 European countries. The list of these countries and data on released amounts of Vigabatrin originating from sales are summarized in the table below:

Table 1 - Products containing vigabatrin as drug substance in EU

COUNTRY	2010	2011	2012	2013	2014	2015	Growth rate 2010 - 2015
AUSTRIA	114.95	113.5	109.5	108	110.63	110.2	-4.13
BELGIUM	317.11	292.94	284.62	270.87	274.53	273.48	-13.76
CZECH	182.8	149.05	135.4	166.6	192.35	191.61	4.82
ESTONIA	7.85	5.35	5.05	1.95	4.2	4.18	-46.7
FINLAND	119.85	102.05	90.95	93.1	85.98	85.65	-28.54
FRANCE	2,236.13	2,063.56	2,035.24	1,966.38	1,898.12	1,890.86	-15.44
GERMANY	1,300.30	1,302.36	1,319.63	1,339.88	1,279.30	1,270.43	-2.3
GREECE	127.85	138.39	95.03	124.85	124.8	124.32	-2.76
HUNGARY	274.45	261.55	245.5	261.55	260.75	259.75	-5.36
IRELAND	121.63	126.18	129.25	123.93	123.35	122.88	1.03
ITALY	2,902.72	2,812.91	2,897.06	2,997.35	2,997.02	2,985.55	2.85
LATVIA	3.15	0	0	0	1.58	1.57	-50.19
LITHUANIA	8.55	1.25	1.35	1.15	6.5	6.48	-24.27
LUXEMBOURG	10.45	10.85	10.55	11.6	11.9	11.85	13.44
NETHERLANDS	211.45	210.33	192.53	185.3	174.1	173.43	-17.98
NORWAY	38.07	39.16	37.44	38.12	40.71	40.56	6.52
POLAND	2,217.43	2,116.65	1,795.53	1,753.38	1,777.85	1,770.70	-20.15
PORTUGAL	450.48	412.53	411.21	387.15	380.43	378.97	-15.87
SLOVAKIA	77.05	82.1	95.2	122.1	96.95	96.58	25.35
SLOVENIA	40.9	46.2	42.05	39.6	45.65	45.48	11.19
SPAIN	808.26	761.47	757.93	765.35	787.83	784.82	-2.9
SWEDEN	171.53	155.05	148.8	151.33	137.05	136.53	-20.4
UK	1,337.35	1,150.95	1,128.43	1,129.50	1,145.88	1,141.49	-14.65
EUROPE total	**13,080**	**12,354**	**11,968**	**12,039**	**11,957**	**11,907**	**-8.97**

The Applicant intends to market Kigabeq 100 mg and 500 mg, soluble tablets only in selected countries among the ones in which Sabril is already marketed and indicated in the table above. The Applicant does not plan to commercialize in the 6 other European countries where Sabril is not marketed, i.e. Denmark, Croatia, Romania, Bulgaria, Malta, or Cyprus.

No new indications and no different posology recommendations are claimed for the drug product. Thus, approval of the drug product in question in Europe will only lead to redistribution of the market share but not to an increase of the total amount of released Vigabatrin. Vigabatrin is freely soluble in water with an experimental solubility of 55.1 mg/mL. Accordingly, the substance is characterised by the very low log KOW of -2.16. A screening for persistence, bioaccumulation and toxicity according to the EU TGD is therefore not required.

Thus, a phase I ERA and phase II ERA, if applicable, are not justified for Kigabeq 100 mg and 500 mg, soluble tablets.

The Applicant commits to re-evaluate the environmental risk after granting of marketing authorisations, if ORPHELIA PHARMA intends to commercialize the medicinal product in a country where vigabatrin is not on the market.

2.5.6. Discussion on non-clinical aspects

No non-clinical studies have been performed for this MAA, which is acceptable according to Article 10(3) Hybrid Application under Directive 2010/83/EC and the relevant nonclinical information on the pharmacology, pharmacokinetics and toxicology can be provided by means of an overview of the

literature. In the CHMP's view the overview provided by the applicant sufficiently describes the nonclinical aspects for the Kigabeq Soluble tablets 100 mg & 500 mg.

The Applicant revised and updated the nonclinical overview and presented new and highlighted already existing studies conducted in immature animals. The CHMP is of the opinion that the absence of further pre-clinical studies in pre-mature animals is considered acceptable given that vigabatrin is used for decades in the proposed indications in children and infants and its safety and efficacy profile is well known in the paediatric population.

The Applicant intends to market Kigabeq 100 mg and 500 mg, soluble tablets only in selected countries among the ones in which Sabril is already marketed. Thus, in the CHMP view a phase I ERA and phase II ERA, if applicable, are not required for Kigabeq 100 mg and 500 mg, soluble tablets and the ERA is expected to be similar and not increased. The Applicant is recommended to re-evaluate the environmental risk after granting of marketing authorisation, if ORPHELIA PHARMA intends to commercialize the medicinal product in a country where vigabatrin is not on the market yet.

2.5.7. Conclusion on the non-clinical aspects

The overview provided by the applicant sufficiently describes relevant nonclinical information on the pharmacology, pharmacokinetics and toxicology as well as ERA, for the Kigabeq Soluble tablets 100 mg & 500 mg. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary by the CHMP. The Applicant is recommended to re-evaluate the environmental risk after granting of marketing authorisation, if ORPHELIA PHARMA intends to commercialize the medicinal product in a country where vigabatrin is not marketed yet as active ingredient of a product authorized for the same indications.

2.6. Clinical aspects

2.6.1. Introduction

This is an application for soluble tablets containing vigabatrin. To support the marketing authorisation application the applicant conducted a bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**) in its current version is of particular relevance.

GCP

According to the statement included in the study report, the bioequivalence study was carried out in accordance with the Declaration of Helsinki (1964) as modified in Fortaleza (2013), the recommendations on Good Clinical Practice (ICH E6) and the applicable French regulatory requirement(s).

The applicant has provided a statement to the effect that SoluWest- Acceptability study conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

According to the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) two medicinal products containing the same active substance can be considered bioequivalent

if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.

The applicant sought a BCS-based biowaiver for Kigabeq 100 mg and 500 mg soluble tablets. According to CPMP/EWP/QWP/1401/98 Rev. 1/Corr** the following conditions have to be met:

a. Drug substance: justification for BCS class I categorization of vigabatrin

b. High solubility: solubility is about 300 mg/mL in aqueous medium at pH 1.2, 4.5 and 6.8, i.e. much higher than the solubility of 8mg/mL (= 2g of vigabatrin dissolved in maximum 250 mL of aqueous medium) required for BCS class I classification

c. Complete absorption (i.e. measured extent of absorption ≥ 85%) based on preclinical data comparing PK after IV and oral administration in dogs, mass balance study in healthy human volunteers and published literature review

The guideline on the investigation of bioequivalence states that the BCS -based biowaiver approach is meant to reduce the burden of in vivo bioequivalence studies. First of all, according to guideline, applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

The dissolution profile of Kigabeq was performed for the range of pH 1.2, 4.5 & 6.8. It was demonstrated that both the test and reference formulation are releasing more than 85 % of the drug product within 15 minutes, hence classifying the formulation as a very rapidly releasing one. The literature data indicates that vigabatrin is generally accepted as a water-soluble compound which is rapidly and completely absorbed from the gastrointestinal tract (Frisk-Holmberg et al. 1989; Sabers et al. 1992; Saletu et al., 1986). Soluble tablets of Kigabeq contain mannitol, crospovidone and sodium stearyl fumarate as excipients.

The high aqueous solubility of vigabatrin across the pH range from 1 to 7 classifies vigabatrin as BCS class I drug, thus supporting the BCS biowaiver claim. However, the CHMP raised concerns regarding the potential differences in bioavailability between Sabril and Kigabeq, resulting from the differences in excipients that might affect absorption. Kigabeq, in contrast to Sabril, contains mannitol which is known and mentioned in the scientific guidelines as a compound which can modify intestinal absorption.

According to scientific guidelines, excipients that might affect bioavailability, such as sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be qualitatively and quantitatively the same in the test product and the reference product. Their possible impact on different factors like gastrointestinal motility, susceptibility to interactions with the drug substance (e.g. complexation), drug permeability or interaction with membrane transporters should be identified. It is acknowledged that mannitol can increase gastrointestinal motility as a consequence of its osmotic effect, thereby reducing the gastrointestinal transit time, which in turn can reduce drug absorption. Given the lack of direct evidence that the differences (qualitative) in excipients (i.e. mannitol content in Kigabeq) do not translate into differences in vigabatrin absorption from Sabril and Kigabeq, the CHMP considered that the BCS biowaiver conditions were not fulfilled for Kigabeq as it was unclear to which extent mannitol may affect vigabatrin absorption.

In order to address the CHMP's concern the applicant submitted the results of a bioequivalence study conducted with the highest strength (500 mg). As already mentioned, the applicant applied for marketing authorization for two different strengths of vigabatrin containing soluble tablets: 100 mg and 500 mg. As Kigabeq is administered as an oral solution and the composition of 100 mg and 500 mg soluble tablets being homothetic, in vivo bioequivalence study waiver was sought for the lower strength of 100 mg as all bio-waiver criteria specified in chapter 4.1.6 of the EMA Guideline on the Investigation of Bioequivalence

(CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are fulfilled, i.e.

a) both strengths are manufactured by the same manufacturing process;

b) the qualitative composition of both strengths is the same;

c) both strengths show a quantitatively proportional composition and

d) both strengths show appropriately similar in-vitro dissolution characteristics

The CHMP assessment of the bioequivalence study and the proposed biowaiver for the 100 mg are detailed in the sections below.

Clinical studies

Table 2 - Tabular overview of clinical studies

Type of study	Study identifier	Localization of study report	Study objective	Study design	Treatments	Numer of subjects	Healthy subjects	Duration of treatment	Study status
BEQ study	OP101 216.ORH	m5-3-1-2	Comparative bioavailability of S(+)-Vigabatrin after single dose administration (fasting conditions) of the test product Vigabatrin 500 mg soluble tablet and Sabril 500 mg granules for oral solution (sachet), 500 mg administered	Randomised, open-label, 2-treatment, 2-period, crossover study, at one study site, pivotal study, oral administration under fasting conditions	(Test: 500 mg soluble tablet, oral administration, [batch 16.92.042]); (Ref: Sabril 500 mg granules for oral solution (sachet), oraladministration [batch 6810])	20	20	One dose/treatment	completed

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Reports of efficacy and safety studies *Study reports of uncontrolled clinical studies*									
Acceptability	TGO-VGB-III-01	Module 5.3.5.2	Primary objective: To describe the adherence to the new soluble tablet formulation of vigabatrin (Vigabatrin ORPHELIA Pharma soluble tablets) Secondary objectives: To evaluate the adherence to, the ease of use and the palatability of the new vigabatrin formulation and Sabril™ granules for oral solution, to evaluate the treatments' safety and tolerance, as well as the pharmacokinetics of vigabatrin and to evaluate taurine levels in children treated with vigabatrin.	Uncontrolled, observational, non-randomized, open-label, multi-centric acceptability study	Test product: Vigabatrin ORPHELIA Pharma 100 mg and 500 mg scored soluble tablets for oral administration to be administered at a dose of 50 to 100 mg/kg/day Reference product: Sabril™ granules for oral solution, 500 mg sachets to be administered at a dose of 50 to 100 mg/kg/day	38 patients enrolled	Boys and girls with diagnosed infantile spasms (IS) or pharmaco-resistant partial onset seizures (POS), aged 1 month to 6 years	Vigabatrin ORPHELIA Pharma soluble tablets: 84 days (mean effective exposure79.5 days) Sabril™: 14 days (mean effective exposure: 17 days)	completed, full

2.6.2. Pharmacokinetics

The applicant has provided an overview of the pharmacokinetics of Vigabatrin, based on the literature, in order to support relevant sections of the SmPC.

Vigabatrin is rapidly and almost completely absorbed from the gastrointestinal tract and the time to peak concentration is 0.5 - 2 h, with a serum half-life of 5 to 8 hours in adults. In children, the time to peak concentration is 1.3 to 2.4 hours, with a serum half-life of about 5.5 hours. In elderly patients, absorption was reported to be delayed. Area under plasma concentration-time curves (AUC) indicated dose-linear pharmacokinetics. Food administration does not alter the extent of vigabatrin absorption. There is no accumulation of vigabatrin upon multiple dosing in adults as well as in children and there are no

significant differences in the pharmacokinetic parameters between healthy volunteers and adults with epilepsy.

Following oral administration, vigabatrin is almost completely absorbed with dose-proportional and linear pharmacokinetics. Due to its hydrophilic character, vigabatrin is widely distributed throughout the body with a high volume of distribution of [R,S]- vigabatrin at steady-state of approximately 0.8 L/kg, a value that is similar to total body water (0.6 L/kg). Although there is no report of tissue distribution in humans, vigabatrin enters the central nervous system (CNS) of patients with epilepsy.

Vigabatrin is eliminated primarily unchanged by renal excretion, with a plasma terminal half-life of 5-7 h. Approximately 70% of a single oral dose is recovered as unchanged in the urine in the first 24 hours post-dose. The mean percentage of 14C recovery in urine was found to be 65.4% (vs. 82.0% for unchanged vigabatrin). Urinary metabolites of vigabatrin accounted for less than 5% of the vigabatrin dose. The mean percentage of 14C recovery in faeces was only 1%. Metabolism vigabatrin is not bound to plasma proteins neither it is metabolised by hepatic enzymes. No metabolites have been identified. Therefore, it was concluded that vigabatrin is not significantly metabolised. Since vigabatrin is neither metabolised by the liver microsomal oxidase nor bound to plasma proteins, pharmacokinetic interactions are unlikely. vigabatrin is associated with very few drug interactions. Drug interactions with vigabatrin are few and generally modest in degree. These drug interactions are not clinically significant and do not require dose adjustment for vigabatrin or concomitant medications. The pharmacokinetic properties of vigabatrin were adequately described in the proposed SmPC.

In addition since the CHMP considered that the BCS biowaiver conditions were not fulfilled the applicant has submitted the results of a bioequivalence study described below.

Study OP101216.ORH: Bioequivalence study of vigabatrin ORPHELIA Pharma 500 mg soluble tablets and Sabril 500 mg granules for oral administration

Methods

Study design

ORPHELIA conducted a clinical bioequivalence (BE) trial between Kigabeq 500 mg soluble tablets and the reference product Sabril 500 mg, granules for oral solution to provide meaningful documented evidence that the amount of mannitol contained in the applicant's formulation is too low to significantly alter gastrointestinal motility in vivo.

The study entitled "Bioequivalence study of vigabatrin ORPHELIA Pharma 500 mg soluble tablets and Sabril 500 mg granules for oral administration" (EudraCT number 2017-000038-67) was conducted between April 4th and August 8th, 2017 in collaboration with the CRO Eurofins-Optimed (France).

The study was an open label, randomized, crossover, 2 periods study in 20 healthy male/female volunteers receiving either 500 mg of Kigabeq soluble tablets or Sabril granules for oral solution, as single oral administration.

Test and reference products

Dose: A single 500 mg dose of each product was selected. This dose has been selected for both feasibility reasons (allowing a high enough plasma concentration to allow for accurate measurements), and ethical reasons. Since vigabatrin is a retinal-toxic drug upon long-term exposure, it was deemed unethical to treat healthy volunteers with a full therapeutic dose of vigabatrin. A 500 mg dose is about 1/5 of the adult

therapeutic dose and was considered to be safe for administration to healthy volunteers. This was assessed and confirmed by the Ethical Committee which reviewed the BE clinical trial protocol. This approach is moreover also in line with the relevant EMA BE Guideline.

Table 3 - Test and reference product information

Product Characteristics	Test Product	Clinical Reference Product
Name	Vigabatrin ORPHELIA Pharma 500 mg soluble tablets	Sabril 500 mg granules for oral solution
Strength	500 mg	500 mg
Dosage form	Soluble tablet	Granules (Sachet)
Manufacturer	ORPHELIA Pharma, France	Sanofi Aventis, France
Batch number	16.92.042	6810
Batch size (Biobatch)	100,000 soluble tablets	-
Expiry date (Retest date)	05/2017*****	05.2019 ******
Member State where the reference product is purchased from	-	France
This product was used in the following trials	OP101216.ORH	OP101216.ORH

***** *Retest date. The shelf-life of the batch 16.92.042 has been extended to 24 months from manufacturing date (05/2016)*

****** *Expiry date*

Population(s) studied

As mentioned above, the study was conducted in adult healthy volunteers. The reasoning for the choice of population is provided below:

1) Adult vs. paediatric populations.

Even if Kigabeq is indicated in the paediatric population only, it was judged unethical to undertake a BE study in children. An adult population was thus employed and the results are considered fully predictive also for the target population as proposed in the SmPC. This approach is considered in line with EMA BE guidline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)

2) Patients vs. healthy volunteers.

Recruitment of an adult patient's population was first evaluated. Such population would have been composed of patients treated with Sabril for refractory partial epilepsy (focal epilepsy). However, several hurdles were identified:

- Such population is extremely scarce, the primary indication of Sabril being infantile spasms. Given the rarity of these patients, recruitment would have been extremely slow.

- Adult patients are most often treated with Sabril tablets, which is not the reference product of Kigabeq.

The design of the BE trial would have required to switch patients from Sabril tablets to Sabril granules for oral solution, then to Kigabeq, then back to Sabril tablets. It was deemed to be complicated and unethical.

- Considering the previous experience with the recruitment of stabilized epilepsy patients in the SoluWest acceptability study (80% of refusal to participate), it was believed that enrolling stabilized epilepsy patients in a BE trial would have been very difficult.

For these reasons, the option to enroll epileptic patients already treated with Sabril was abandoned and it was decided to conduct a BE trial in healthy volunteers. This approach is considered in line with the aforementioned regulatory guideline.

Sample size

According to previous studies, Cmax has the largest intra-subject variability (CV=15%) and thus it is sensible to power the study based on this value. It follows that 12 subjects completed the study would be required to have 90% power to demonstrate bioequivalence within the limits of 80% to 125%, assuming that the two formulations are equivalent.

However, it should be noted that this intra-subject variability is based on a small sample size so it may not be an accurate reflection of the true population within-subject. That is why a CV of 20% is taken into account to compensate lack of accuracy. Based on this value, a sample size of 20 subjects completed the study without deviation affecting pharmacokinetic criteria evaluation is needed to have 90% power to demonstrate bioequivalence within the limits of 80% to 125% (Julious 2004, Statis .Med. 23: 1921-1986).

Main inclusion criteria

- Healthy male and female subject, aged between 18 and 50 years inclusive;
- Females of childbearing potential/Sexually active males with partner of childbearing potential: commitment to consistently and correctly use an acceptable method of birth control for the duration of the trial and for 1 month after the last study drug administration;
- Females of non-childbearing potential: either surgically sterilized or at least 1 year postmenopausal;
- Non breast-feeding female and negative pregnancy test at screening baseline;
- Non-smoker subject or smoker of not more than 5 cigarettes a day;
- Body Mass Index (BMI) between 18,5 and 25 kg/m2 inclusive;
- Considered as healthy after a comprehensive clinical assessment (detailed medical history and complete physical examination);
- Normal Blood Pressure (BP) and Heart Rate (HR) at the screening visit after 10 minutes in supine position or
- considered NCs by investigators;
- Normal ECG recording on a 12-lead ECG at the screening visit or considered NCs by investigators;
- Laboratory parameters within the normal range of the laboratory (hematological, blood chemistry tests, urinalysis).

- Individual values out of the normal range could be accepted if judged clinically non relevant by the Investigator;
- Normal dietary habits.

Analytical methods

Enantiomers: According to the EMA guidance (i.e. chapter 4.1.5 of the EMA BE NfG) an achiral analytical method would apparently be sufficient. Nevertheless, to be on the safe side and to prevent any discussions on the suitability of an achiral methodology it was decided to measure the plasma concentrations of the active S(+) enantiomer of vigabatrin by use of a suitably validated chiral bioanalytical procedure.

The analytical method for the determination of vigabatrin in human plasma seems to be described adequately; the validations were performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)". Acceptance criteria are in a plausible range. The analytical methods used are acceptable and appropriate. The calibration curves are appropriate and the stability testing supports the conditions the samples were exposed to during collection and testing.

The storage of the study samples was 53 days and is in line with the documented stability of S(+)-Vigabatrin in plasma of up to 95 days.

Robustness, reproducibility and reliability of the bioanalytical method's results are also indicated by success rate of valid analytical runs and the results of incurred sample reanalysis which confirmed the initial analytical results by 97.50%.

Pharmacokinetic variables

Following the selection of an adult healthy volunteer's population, the design of the envisioned BE trial was as follows: an open label, randomized, crossover, 2 periods study comparing Cmax and AUC0-t of Kigabeq and Sabril granules for oral solution.

Cmax and AUC0-t of the S(+) enantiomer of vigabatrin were selected as primary PK parameters to be compared as per EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

The secondary PK parameters were AUC0-inf, tmax, λz, t1/2 and residual area of the S(+) enantiomer of vigabatrin as recommended by the relevant EMA Guideline.

Blood samples were taken at the following time points: pre-dose sample; post-dose samples: 15 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 8 h, 12h, 16h, 24h and 36h.

The safety parameters were physical examination, vital signs, adverse events, concomitant treatments, ECG, visual field (by perimetry) and laboratory examinations.

Statistical methods

The statistical analysis consisted in individual data listings and descriptive statistics performed by Eurofins Optimed.

All individual data for all enrolled subjects were presented in data listings, sorted by subject within sequence. Demographic and baseline characteristics data were summarized by sequence and overall subjects. On-treatment data were summarized by treatment and visit.

For parameters with evaluation before dosing and in case of rechecked value(s) for any subject, only the last observation was used in descriptive statistics and derivations of other parameter values. After dosing, only observations planned in the protocol were used in descriptive statistics.

Drug plasma concentrations were measured and pharmacokinetic parameters were calculated only for the active S(+) enantiomer of vigabatrin.

The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the geometric means (test/reference) for the parameters under consideration Cmax and AUC0-t). This method is equivalent to two one-sided tests with the null hypothesis of bio-inequivalence at the 5% significance level.

Cmax and AUC0-t determined from S(+) enantiomer of vigabatrin plasma concentrations were described by treatment.

The pharmacokinetic parameters (Cmax and AUC0-t) under consideration were analyzed using ANOVA. The data were transformed prior to analysis using a logarithmic transformation. A confidence interval for the difference between formulations on the log-transformed scale was obtained from the ANOVA model. This confidence interval was then back-transformed to obtain the desired confidence interval for the ratio on the original scale. A non-parametric analysis was not acceptable.

The statistical analysis took into account sources of variation that could be reasonably assumed to have an effect on the response variable. The terms to be used in the ANOVA model are sequence, subject within sequence, period and formulation. Fixed effects, rather than random effects, should be used for all terms.

Assessment of bioequivalence was based upon the 90% 2-sided confidence interval of the geometric means ratio between test product and reference product for the AUC0-t and Cmax parameters. Bioequivalence was concluded if the 90% 2-sided confidence intervals were contained within the acceptance interval [80% ; 125%].

Results

- **Pharmacokinetic (PK) results**

Table 4 - Pharmacokinetic parameters for S-Vigabatrin (non-transformed values)

	Test		Reference	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
AUC(0-t)	29.39	±3.61	29.56	±5.06
AUC(0-∞)	30.97	±3.73	31.15	±5.10
Cmax	6.0410	±1.4666	5.9560	±1.8242
Tmax*	0.71	±0.32	0.69	±0.33

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 5 - Statistical analysis for S-Vigabatrin (ln-transformed values)

Pharmacokinetic parameters	Geometric Mean Ratio Test/Ref	90.00% Confidence Intervals	CV (%)
AUC_{0-t}	100.14	96.95 - 103.43	6
C_{max}	103.06	96.96 - 109.54	11
For information only:			
AUC_{0-inf}	99.99	97.27 - 102.79	5

The results obtained unambiguously satisfy the bioequivalence criteria of the relevant EMA BE Guideline. Hence, the trial demonstrated bioequivalence between Kigabeq 500mg soluble tablets and the reference product Sabril 500 mg granules for oral solution.

- **Safety data**

No serious adverse events were reported during this trial. The adverse events were not life threatening or required the subjects to be hospitalized. After study drug intake, 7 subjects showed 10 AEs -5 after Test treatment and 5 after Reference treatment. The most frequent AE, which was reported after study drug intake was headache. All AEs reported after study drug intake resolved completely. No subject dropped out due to AEs.

No clinically relevant findings were observed in clinical examination, biological, vital signs and ECG parameters. No abnormal findings were observed in any subject at follow up visit for visual field test.

It was concluded that single oral administration of the test product Kigabeq (denoted thereafter "VGB-ST") or the reference product Sabril was well tolerated.

Conclusions

The applicant has initially claimed a BCS based biowaiver for its vigabatrin formulation arguing that the presence of mannitol in the formulation is sufficiently low that a clinically meaningful alteration of the gastrointestinal motility is fairly unlikely. The bioequivalence was confirmed by the results gained in-vivo in the course of a single dose bioequivalence study of the applicant's formulation in comparison to the reference drug product in healthy subjects under fasting conditions, since the T/R point estimates and derived 90% confidence intervals of the rate and extent of absorption metrics of S-Vigabatrin were entirely contained within the common acceptance margin (i.e. 80.00 to 125.00%) for bioequivalence.

2.6.3. Discussion on clinical pharmacology

To support the application, the Applicant has submitted one bioequivalence study (BE). The test product (Kigabeq 500 mg soluble tablets) and the reference product (Sabril 500 mg, granules for oral solution). The study was an open label, randomized, crossover, 2 periods study in 20 healthy male/female volunteers receiving either 500 mg of Kigabeq soluble tablets or Sabril granules for oral solution, as single oral administration under fasting conditions. The applicant presented an explanation regarding the choice of the population for the BE study. In the CHMP's view the choice of the population i.e. adult, healthy volunteers instead pediatric population with infantile spasm is considered appropriate and in line with the current guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

The methodology related to sample size calculation and statistical evaluation of bioequivalence of two products was clearly presented and properly discussed. Parameters chosen for sample size calculations were appropriate and in line with the requirements of the BE guideline. AUC0-tlast and Cmax were considered as primary decision criteria for bioequivalence assessment.

The sampling periods are acceptable with sample time points around Tmax for vigabatrin and with an adequate wash-out period (at least 7 treatment free days) at greater than five times the t1/2 for vigabatrin. The sampling frequency enabled an adequate estimation of Cmax. The sampling schedule covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure.

The population studied is appropriate and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). According to the applicant's calculation of study sample, it appeared that 12 subjects would be sufficient to demonstrate the bioequivalence of Kigabeq and Sabril. However, bearing in mind that intra-individual variability of AUC and Cmax was based on a small sample size so it may not be an accurate reflection of the true population within-subject. Therefore a CV of 20% was taken into account. The employed approach is considered acceptable. Twenty healthy subjects (55% female and 45 % male), aged ≥ 18 years, were randomised. The mean age was 35 years, ranging from 18 to 50 years.

The analytical method for the determination of vigabatrin in human plasma is described adequately; the validations were performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)". Acceptance criteria are in a plausible range. The analytical methods used are acceptable and appropriate. The calibration curves are appropriate and the stability testing supports the conditions the samples were exposed to during collection and testing.

The pharmacokinetic variables are considered adequate. Acceptance range for bioequivalence was 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for Cmax and AUC0-tlast of vigabatrin. The appropriate variables were measured and the employed statistical methodology is considered acceptable. Plasma samples and ISR were analysed within 53 days after storage at the target temperature of -80°C. The long term stability period validated for S-Vigabatrin was up to 95 days at -80°C.

It was observed that maximum exposure, represented by arithmetic mean Cmax-values, was similar for both products with 6.0410 ug/ml for Kigabeq and 5.9560 ug/ml for Sabril. Extent of bioavailability, represented by arithmetic mean AUC(0-t) -values, was 29.39 h*ug/ml for Kigabeq and 29.56 h*ug/ml for Sabril.

The mean time points of maximum exposure, represented by median values of tmax, were comparable for both treatments (0.71 h for Kigabeq and 0.69 h for Sabril).

For the primary pharmacokinetic parameter AUC0-tlast a point estimate of 100.14 % with an affiliated confidence interval of 96.95 – 103.43 % was calculated. For Cmax, which was also defined as primary criterion, a point estimate of 103.06% with an affiliated confidence interval of 96.96 – 109.54 % was calculated. Thus, both confidence intervals were within the pre-set acceptance limits of 80.00 – 125.00 %, and bioequivalence of Kigabeq and Sabril was demonstrated with regard to AUC0-tlast and Cmax of the compound vigabatrin.

A total of 20 subjects were evaluated for safety. Both products were found to be safe and well tolerated.

Justification for requesting bio-waiver for the lower strength i.e. Kigabeq 100 mg soluble tablets was prepared according to general bio-waiver criteria as specified in the Guideline on the Investigation of

Bioequivalence. Kigabeq 100 mg satisfies the conditions for bio-waiver of in vivo bioequivalence study with Kigabeq 500 mg soluble tablets (both strengths are manufactured by the same manufacturing process, the qualitative composition of both strengths is the same, both strengths show a quantitatively proportional composition and both strengths show appropriately similar in-vitro dissolution characteristics.)

Presented BE study was designed and conducted according to the recommendations set in the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Based on the results obtained in the bioequivalence study (EudraCT-No.: 2017-000038-67), the soluble tablets of vigabatrin (VGB-ST) (Test) 500mg and Sabril 500mg granules for oral administration (Reference) in healthy adult subjects, are considered bioequivalent.

Moreover the applicant has provided an overview of the pharmacokinetics and pharmacodynamics of vigabatrin, based on the literature data, in order to support relevant sections of the SmPC.

An in vitro dissolution study was performed to compare the dissolution profiles of Kigabeq 100 mg and 500 mg soluble tablets and Sabril 500 mg granules for oral solution in order to support its BCS biowaiver claim in line with current regulatory guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**). Of note, the rightfulness of the BCS based biowaiver has been definitely affirmed by demonstrating in-vivo bioequivalence between the applicant's 500 mg soluble tablets and the reference product (Sabril). So, the role of the BCS biowaiver claim is merely supportive for the current application. Nevertheless, for the sake of completeness the submitted information in support of the reliability of the in-vitro dissolution study in support of the BCS biowaiver is discussed below.

The protocol was set in accordance with the EMA Guideline on Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**. and the dissolution profile was evaluated using a dissolution paddle apparatus at three pH conditions (1.2, 4.5 and 6.8).

Due to the very rapid dissolution profile of Kigabeq soluble tablets, vigabatrin contents were assayed at 1 and 3 minutes time points. All samples fully dissolved within 3 minutes at any pH demonstrating the equivalence of dissolution profiles between Kigabeq 100 mg and 500 mg soluble tablets and Sabril 500 mg granules for oral solution.

2.6.4. Conclusions on clinical pharmacology

To summarize, the applicant has initially claimed a BCS based biowaiver for its vigabatrin formulation arguing that the presence of mannitol in the formulation is such low that a clinically meaningful alteration of the gastrointestinal motility is fairly unlikely. This appraisal was confirmed by the results gained in-vivo in the course of a single dose bioequivalence study of the applicant's formulation in comparison to Sabril as reference drug product in healthy subjects under fasting conditions, since the T/R point estimates and derived 90% confidence intervals of the rate and extent of absorption metrics of S-Vigabatrin were entirely contained within the common acceptance margin (i.e. 80.00 to 125.00%) for bioequivalence decision making.

The Applicant has performed in vitro dissolution tests comparing the test and reference bio-batches used in bioequivalence study. More than 85% of the labelled amount of the drug was released within 15 minutes from each tested formulations in all three mediums.

In addition, the comparative dissolution test regarding the biowaiver for vigabatrin 100 mg strength was conducted according to recommendations of the Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr**. Similarly to dissolution of test and reference bio-batches used in bioequivalence study, more than 85% of the drug was released within 15 minutes from each tested formulations in all three mediums: 0.1N

Hydrochloric acid (Release media), pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer, the dissolution profiles can be considered as similar. Therefore, a bio-waiver for the 100 mg strength is granted.

Based on the presented bioequivalence study Kigabeq 500mg soluble tablets is considered bioequivalent with Sabril 500 mg granules for oral solution.

The results of study OP101216.ORH with Kigabeq 500mg soluble tablets formulation can be extrapolated to the lower strength 100 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.6.5. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. The applicant has provided an overview of the pharmacodynamics of vigabatrin, based on the literature, in order to support relevant sections of the SmPC.

Vigabatrin was specifically designed to increase brain GABA levels by inhibiting catabolism of this neurotransmitter. It replaces GABA as substrate for GABA transaminase (GABA-T). The resultant increased level of GABA leads to a reduction in seizure activity. Vigabatrin acts as an indirect GABA agonist, which propagates its clinical effects via selective, irreversible inhibition of GABA transaminase, thus raising GABA levels in the brain. Increased levels of GABA lead to a reduction of seizure activity whereby vigabatrin is effective for the treatment of various forms of epilepsy including infantile spasms and resistant partial epilepsy in children. Serum concentrations of vigabatrin do not correlate with efficacy. The duration of the effect (pharmacodynamics) of the drug is dependent on the GABA transaminase re-synthesis rate, and thus vigabatrin shows an extended functional half-time. In children with refractory epilepsy seizure reduction was correlated with dosage but not with steady-state plasma concentrations or GABA-T inhibition. The pharmacodynamic properties of vigabatrin are adequately reflected in the proposed SmPC.

2.6.6. Clinical efficacy

Kigabeq Soluble tablets (100 mg & 500 mg) is an hybrid application of the reference medicinal product Sabril and is designated to have two of the same indication and posology as Sabril.

Summary of main efficacy results

No new efficacy studies were performed by the applicant. Literature data support the use of vigabatrin in paediatric patients in the proposed indications. The dosage recommendations given in the SmPC appear appropriate based on the review of published literature

The possible efficacy of vigabatrin in IS, particularly in IS due tuberous sclerosis (TSC), has been suggested very early on in the development of vigabatrin based on an observational study as adjunctive therapy. Since then, several studies have demonstrated the effectiveness of vigabatrin as first-line monotherapy in children with IS. Most trials randomly compared vigabatrin to hormonal treatment (ACTH or oral cortico-steroids). In IS due TSC, vigabatrin proved to be more efficient (Chiron et al 1997), so that vigabatrin has been recommended as first choice in this context for more than 15 years on. In IS due to other etiologies, vigabatrin was shown less efficient at short term (Lux et al 2004), but equivalent at long term (Lux et al, 2005; Darke et al, 2010), and recent data plaid for a combined hormonal/vigabatrin therapy (O'Callaghan et al, 2017).

Luna et al. (1989) evaluated the efficacy of vigabatrin in paediatric patients (12 – 229 months of age) with refractory epilepsy. Twenty-three patients (38%) showed a reduction of more than 50% in seizure

frequency; 12 patients (20%) experienced a seizure increase; and the remaining 26 did not show significant differences between placebo and vigabatrin treatment. Vigabatrin was particularly efficient in cryptogenic partial epilepsy. The efficacy and safety of vigabatrin in paediatric patients with refractory epilepsy was also studied by a database review of medical records of paediatric patients treated with vigabatrin, either alone or in combination, for three months or more. Vigabatrin reduced seizure frequency by at least 50% in 33.3% of patients with partial seizures, and in 30.6% of patients with primary generalized seizures. Six of the responders with partial seizures had complete resolution of their seizures. A study compared the efficacy and side effects of lamotrigine and vigabatrin as add-on therapy in epilepsies of childhood resistant to conventional drugs. In general, lamotrigine and vigabatrin had similar efficacy, with 30-40% of patients demonstrating significant improvement. Primary generalised tonic-clonic seizures more frequently improved and less frequently worsened with lamotrigine than with vigabatrin.

An open-labelled multicentre study in which patients had experienced a significant benefit from vigabatrin was performed. The purpose of this study was to examine the long-term safety and efficacy of vigabatrin as add-on treatment for drug-resistant epilepsy in patients treated in Europe for over one year. In patients who had demonstrated a significant response to vigabatrin during earlier studies, the same continued efficacy was observed whether the patient had complex partial, secondarily generalised or primary generalised seizures.

Vigabatrin is used as monotherapy for IS (West syndrome) and adjunctive antiepileptic in children with resistant partial epilepsy with or without secondary generalisation, unresponsive to other therapy. Vigabatrin is for oral administration once or twice daily and may be taken before or after meals. The proposed new formulation is additionally also suitable for gastric administration via nasogastric tubes in patients who cannot swallow.

The recommended initial dose of vigabatrin is 50 mg/kg daily, adjusted according to response (Martindale Vigabatrin, 2016). This may be titrated over a period of one day to one week if necessary. Doses of up to 150 mg/kg/day have been used with good tolerability (SmPC Sabril 500 mg, 2016). Resistant partial epilepsy: In children, the recommended starting dose is 40 mg/kg/day. Maintenance recommendations are related to body weight with a maximum recommended dose of 1.5 g/day for a child of 30 kg body weight (SmPC Sabril 500 mg, 2016).

During the procedure the applicant proposed to deviate from the current dose titration recommendations for Infantile spasms given in Sabril's SmPC as indicated below.

Kigabeq 100 mg and 500 mg, soluble tablets (proposed recommendation)	**Sabril 500 mg, granules for oral solution (UK SmPC updated version -14 July 2014)**
The recommended starting dose is 50 mg/kg/day. Subsequent dosing can be titrated by 25 mg/kg/day increments every 3 days up to the maximum recommended dose of 150 mg/kg/day. The maximum recommended dose is 150 mg/kg/day.	The recommended starting dose is 50 mg/kg/day. This may be titrated over a period of one week if necessary. Doses of up to 150 mg/kg/day have been used with good tolerability

The current European Sabril SmPC does not give detailed instructions regarding up-titration. An up-titration may improve the tolerance to the product, as recommended by the Paediatric Epilepsy Research Consortium (PERC), especially with regards to CNS side effects: drowsiness, sedation or hypotonia.

Furthermore, rapid withdrawal of vigabatrin has resulted in an exacerbation of seizures in a few, but

dramatic, cases. Hence, a tapering of the dose may also be beneficial. In both US and Canadian Sabril SmPCs an up-titration with increments of 25-50 mg/kg/day (twice daily) is proposed.

A similar titration scheme is proposed by the British National Formulary for Children (BNFC) which state that the maintenance dose should be "adjusted according to response over 7 days" and by the American Society of health –System Pharmacists (AHFS) drug information which advocate titration steps of: "25-50 mg/kg daily every 3 days up to maximum recommended dose of 150 mg/kg daily".

In published clinical studies (see below table), the titration steps employed were either 25 or 50 mg/kg/day. Duration of titration was either 1 to 3 days for each titration step, or 1 week for the whole titration (with the exception of earlier studies of Chiron et al.)

Table 6 - Clinical trials conducted with vigabatrin in "infantile spasms" in monotherapy

Reference	Trial design and patient number (N)	Dose range mg/kg/d	Titration steps
Chiron et al 1991	Open, prospective ; add-on (70)	<2y : 100-200 >2y : 50-150	50 to 100 to 150 mg/kg/d at at least 1 week intervals
Chiron et al 1997	Randomized, Comparative *vs* HC; monotherapy (11)	150	No titration
Vigevano et al 1997	*Pseudo-randomized vs* ACTH; monotherapy (42)	100-150	100 to 125 to150 mg/kg/d with 3 days titration steps
Villeneuve et al 1998	Open, retrospective, monotherapy (70)	100-150	100-150 mg/kg/d with 8 days titration steps
Appleton et al 1999	Randomized *vs* Placebo, monotherapy (40)	50-150	50 mg/kg/d for 1 day; then 100 mg/kg/d for 2 days then 150 mg/kg/d
Elterman et al 2001 (2010) *Interim (final)*	Randomized single-blind high/low dose monotherapy (High : 67); (Low : 75)	16-38 (low dose) *vs* 100-148 (high dose)	Steps not described, but dose titrated over 7 days (high dose)
Lux et al 2004	Randomized open comparative *vs* ACTH / prednisolone monotherapy (107)	50-150	50 mg/kg/d for 1 day; then 100 mg/kg/d for 4 days then 150 mg/kg/d
Knupp et al 2016	Open, prospective, comparative *vs* ACTH / oral cortico-steroids /others; monotherapy (47)	50-150	50 mg/kg/d for 1 to 3 day; then 100 mg/kg/d for 1 to 3 days then 150 mg/kg/d
O'Callaghan et al 2017	Randomized open Comparative Horm/Horm+VGB; monotherapy (186)	50-150	50 mg/kg/d for 1 day; then 100 mg/kg/d for 3 days, then 150 mg/kg/d

The Applicant proposes to recommend a similar up-titration as the one recommended in the US Sabril SmPC with an incremental dose of 25 mg/kg/day. With regards to the titration period, a 3-day period per titration step (as per the US SmPC) seems justified in regards to the rapidity of action of vigabatrin and the necessity to implement a relatively rapid titration scheme in IS, due to deleterious effects of delayed treatment on long-term prognosis.

Furthermore, this 3-day period is in line with the European Sabril SmPC which suggests a 1 week titration period to reach the maintenance dose (that is going from 50 to 100 mg/kg/day in 7 days by adding two 25 mg/kg/day titration steps). It is also in line with the regimen used in clinical studies (see above).

The Scheme below illustrates the proposed titration doses and periods.

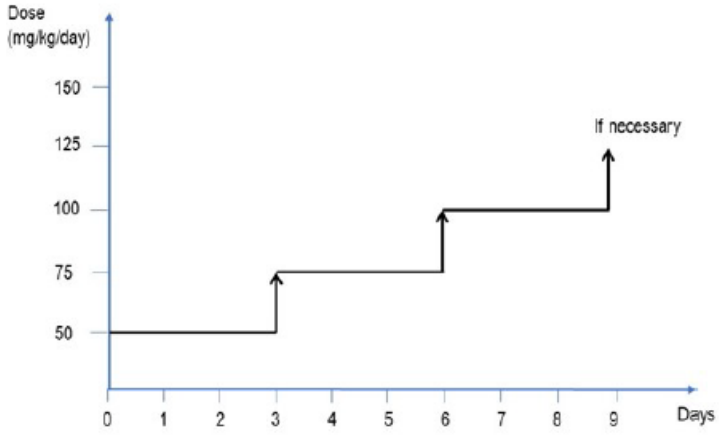


Figure 2: Titration doses and periods

To clarify the titration by incremental dosing steps of 25 mg/kg/day, the SmPC contains a table containing dispensing recommendations adapted to the new formulation and the IS population. Infants with IS are ranging from 1 month to less than 2 years, and weight from 3 kg to a maximum of 16 kg (97th percentile at 2 years). Hence, the table would highlight the 50 mg/kg/day starting dose and the two subsequent titration steps of 75mg/kg/day and 100 mg/kg/day.

Discussion on clinical efficacy

Based on the literature, the applicant has provided a clinical overview which in a detailed way sums up the known facts concerning the efficacy of vigabatrin in the treatment of Infantile Spasms, regardless of underlying etiology as well as the anticonvulsant effect of vigabatrin as add-on therapy in patients with epilepsy not satisfactorily controlled by conventional therapy, in order to support relevant sections of the SmPC.

In the CHMP's view the applicant's proposals regarding the 25 mg/kg/day dose increments and 3-day titration period in infantile spasms are justified by the potential to improve the tolerance to the product and take into account the clinical practice recommendations, as well as the titration recommendations employed in published clinical studies. Moreover this proposal is in line with the European Sabril SmPC which suggests a 1 week titration period to reach the maintenance dose (that is going from 50 to 100 mg/kg/day in 7 days by adding two 25 mg/kg/day titration steps). In addition in order to clarify the titration by incremental dosing steps of 25 mg/kg/day, a detailed dose dispensing/titration guidance is presented din a tabulated manner in section 4.2 of the SmPC. The guidance is adapted to the IS population ranging from 1 month to less than 2 years, and weighting from 3 kg to a maximum of 16 kg (97th percentile at 2 years). The applicant privileged the 100 mg strength for patients with a body weight ≤ 11 kg, to allow maximum accuracy for dose and body weight as well as the necessary flexibility to perform the titration steps. Above a bodyweight of 11 kg a combination of both strengths (100 mg and 500 mg) is necessary to avoid that patients/caregivers have to handle multiple 100 mg tablets. This approach was endorsed by the CHMP.

The dosage recommendations given in the SmPC appear appropriate based on the review of published literature and clinical guidance.

Conclusions on clinical efficacy

Available studies support the use of vigabatrin as monotherapy in IS or as add-on therapy in paediatric patients with epilepsy not satisfactorily controlled by conventional therapy.

2.6.7. Clinical safety

In accordance with the PIP for the proposed product agreed by the EMA on 11th July 2014 (Decision P/0173/2014, Modification Decision P/0271/2015 and P/0083/2017) the applicant conducted two studies as part of the agreed measures:

- One in-vitro study with nasogastric tubes made of different types of polymers was conducted to generate data on the compatibility with reconstituted drug product liquid and to affirm dose recovery after extrusion through the nasogastric feeding tubes and
- An open label, observational acceptability study to evaluate acceptability/palatability, safety and tolerability of the proposed product in children aged 1 month to less than 7 years with seizure disorders.

Study Title: Vigabatrin – Use-study of nasogastric tubes

To exclude the possibility of adsorption and to prove the compatibility of the proposed formulation of Kigabeq with materials commonly used in association with nasogastric feeding in infants and children, the applicant conducted an in vitro study.

This study 'Vigabatrin – Use-study of nasogastric tubes' was initiated on request by EMA as an agreed measure within the PIP with the following purpose: "Generation of data on compatibility with nasogastric tube: dose recovery after extrusion through the nasogastric tube should be demonstrated using rinsing volumes relevant to the target population". The aim of this study was to investigate the compatibility between the liquid of reconstituted drug product in tap water with different plastic devices used for drug administration in clinical practice (e.g. nasogastric tubes, syringes, cups). The chosen approach was to evaluate whether the drug substance vigabatrin is adsorbed on plastic materials used in the course of administration of the reconstituted drug product in tap water, e.g. nasogastric tubes, syringes and cups, and if so, to what extent. The following plastic materials were tested: - Paediatric nasogastric tube Nutrisafe 2 made of Polyurethane (product code: 1362.082, dead volume = 2.30 mL); - Paediatric nasogastric tube Nutrisafe 2 made of Silicone (product code: 2332.082, dead volume = 2.34 mL); - Plastic syringes Nutrisafe 2 made of Polypropylene (seal: polyisoprene); - Plastic cups made of Polypropylene (ISO 7056).

The study was conducted by firstly dispersing 5 x 100 mg soluble tablets of 100 mg strength in 2 mL of tap water at 25°C in the plastic cup. The suspension was stirred for 1 minute, introduced into the nasogastric tube by use of the plastic syringe and left in contact with the tube for T=10 min. The vigabatrin suspension was then recovered in a glass beaker at the other end of the tube and both, the plastic cup and the nasogastric tube, were rinsed with 5 mL of tap water, respectively, and the fluids were combined with the recovered vigabatrin suspension (about 12 mL). After centrifugation an aliquot of the supernatant was suitably diluted with mobile phase of the HPLC method. The concentration of vigabatrin in this liquid was determined after filtration via a validated HPLC/UV method with external calibration. Absence of adsorption of vigabatrin on filter material used (nylon) was documented. The recovered vigabatrin quantity was compared with the theoretical 100% quantity obtained by dispersing 5 x 100 mg soluble tablets in 12 mL of tap water in a glass beaker. The obtained liquid (control solution) was treated in the same way as the test solution. Each experiment was repeated 6 times. Average recovery and RSD were calculated.

The recovered vigabatrin quantities after 10 min disposition within polyurethane or silicone nasogastric tube are close to the recovered vigabatrin quantities obtained with the control solutions (i.e. without contact with plastic cup, syringe and nasogastric tube). The results indicate that there is no relevant

adsorption of vigabatrin on nasogastric tubes made of polyurethane or silicone. Moreover, the results further demonstrate that vigabatrin is also not adsorbed on polypropylene commonly used in the course of preparation of the reconstituted liquid (cup) and in the course of administration (syringe).

Table 7 - Results of vigabatrin amounts (mg) recovered in reconstitution liquid after contact with plastic cup, plastic syringe and a contact of 10 minutes within nasogastric tube versus control solution

		Amount of vigabatrin (mg)		
		Control	**Polyurethane nasogastric tube**	**Silicone nasogastric tube**
Test solution 1		479.8	506.1	508.5
Test solution 2		493.8	501.3	511.5
Test solution 3		483.8	507.2	507.1
Test solution 4		482.5	507.4	506.5
Test solution 5		487.6	500.6	505.0
Test solution 6		479.0	507.0	507.3
Vigabatrin content (mg)	mean	**484.4**	**504.9**	**507.7**
RSD (%)		1.1	0.6	0.4
Recovery comparison control (%)	in with	/	104.2	104.8

Study Title: SoluWest - Acceptability study of a new paediatric form of vigabatrin in infants and children with infantile spasms or pharmaco-resistant partial epilepsy

Methods

Treatments

The applicant conducted SoluWest -an acceptability study of a new paediatric form of vigabatrin in infants and children with infantile spasms or pharmaco-resistant partial epilepsy. This study is part of a Paediatric Investigation Plan (PIP) (EMA-000717-PIP02-13-M02). It was designed as a descriptive, non-randomized, open label multi-centric acceptability study in infants and children, between 1 month and 6 years of age, affected with infantile spasms or pharmaco-resistant partial epilepsy

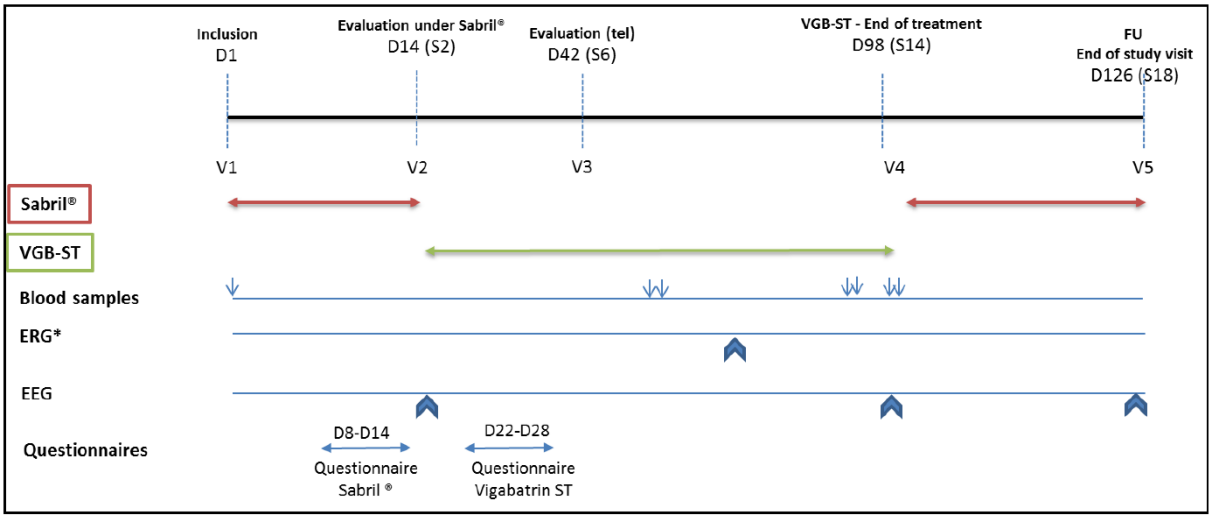
Outcomes/endpoints

The primary objective of the trial was to describe the adherence to Kigabeq. The secondary objectives were:

- Evaluation of the adherence to Kigabeq and to Sabril "granules for oral solution", in terms of treatment unit accountability
- Evaluation of the palatability for Kigabeq and for Sabril "granules for oral solution"
- Evaluation of the ease of use for Kigabeq and for Sabril "granules for oral solution"
- Evaluation of treatments safety and tolerance
- Evaluation of the pharmacokinetic parameters for vigabatrin (by a population PK method)

The study was composed of three successive phases:

- A first "run-in" phase (D1-D14), in which the patient (stabilized under Sabril "granules for oral solution") continued treatment with study Sabril,
- A second "treatment" phase (D15-D98) in which the patient switched to Kigabeq at the same dose and treatment regimen as Sabril. At D99 the patient switched back to Sabril treatment (or another anti-epileptic drug) at investigator's discretion. During the "treatment phase", the concomitant antiepileptic treatments could be changed (dose, type) if necessary, according to clinical practice, but no change in the dose of Kigabeq was permitted,
- A third 'follow-up" phase (D99-D126).



* photopic electroretinograms (ERG) performed as a standard of care, if not performed within the last 6 months.

Figure 3 - Schedule of assessments and study visits

Objectives

Treatment adherence: The adherence to treatment was the primary objective of the trial; it was evaluated by two distinct means:

- For Kigabeq , by the dosing history of the patient using an electronic Medication Event Monitoring System (MEMS) between V2 and V4.

- For Kigabeq and Sabril sachets, by measurement of the unused quantities of treatment for the 2 weeks period between V1 and V2 (Sabril) and the 12 weeks period between V2 and V4 (Kigabeq). The primary

endpoint was the proportion of adherent patients under Kigabeq. Adherence was assessed by measurement of the dosing history of patients using an electronic Medication Event Monitoring System (MEMS).

Adherence was also assessed secondarily by accountability of Kigabeq (number of tablets) and Sabril "granules for oral solution" (number of sachets).

Palatability measurements: The palatability of the treatment was evaluated using a two face visual hedonic scale filled in by the parents and/or by the child, if feasible, on a daily basis. Each "face" of the scale was assigned a score (1 or 2), and the average score was calculated for the group. Palatability was considered good if the average score for the group was at least 1.5 (out of a maximum of 2; Motte et al. 2005). Palatability was evaluated for Kigabeq and for Sabril "granules for oral solution". Palatability was evaluated for 7 consecutive days: from D8 to D14 for Sabril and from D22 to D28 for Kigabeq . Ease of use was evaluated for Sabril « granules for oral solution » and for Kigabeq using two diaries filled by the parents or care-givers for 7 consecutive days: from D8 to D14 for Sabril and from D22 to D28 for Kigabeq.

Time required for preparation of both Kigabeq and Sabril administrations was averaged and compared, together with the global use satisfaction.

Taurine plasma concentrations were measured and a relationship between vigabatrin exposition and taurine plasma levels was to be sought. 1 sample was to be drawn at V4: just before treatment when patient was fasting.

Safety measurements:

- Results of electroretinogram (when available).
- General safety, including:
  - Blood cells count, blood ionogram, serum creatinine, liver function assessment, at V1 and V4.
  - Vital signs (cardiac frequency and blood pressure) at V1, V2, V4 and V5.
  - Adverse events and serious adverse events, at each study visit.

Statistical methods

According to the Applicant's assumptions, the statistical analysis was supposed to include analysis of:

- ✓ **sample size**: The estimation of sample size was derived from literature analyses. The primary end-point is the proportion of adherent patients. The expected adherence was estimated from similar acceptability studies of off-patent drugs for paediatric populations.
- ✓ **main analysis**
  - o treatment adherence: The primary end-point was the individual adherence of patients to Kigabeq. The mean of individual adherence was calculated with a 95% two-sided confidence interval. Standard deviation, median, quartiles, minimum and maximum were also calculated. Adherence by dosing history using MEMS: Individual adherences were evaluated by the number of positive dosing event during the Kigabeq period.
  - o secondary end-points analysis. The secondary outcomes were described with 95% bilateral confidence intervals. Mean, standard deviation, median, quartiles, minimum and maximum were calculated for quantitative outcomes.

- Adherence by tablets and sachets counting. Individual adherences to Kigabeq were also evaluated by measuring the number of unused tablets for the treatment period
- Evaluation of the palatability for Kigabeq and for Sabril “granules for oral solution”
  - Each “face” of the scale was assigned a score (1 for the “bad face” and 2 for the “good face”). Palatability was considered good if the average score for the group was at least 1.5 (out of a minimum of 1 and a maximum of 2; Motte et al. 2005). Palatability was evaluated for Kigabeq and for the Sabril granules for oral solution and compared.
- Evaluation of the ease of use for Kigabeq and for Sabril “granules for oral solution”
- Time required for preparation of both Kigabeq and Sabril administrations was averaged and compared, together with the global use satisfaction.

✓ **safety analysis**

- The safety analysis was performed on the Safety Data Set; it was a descriptive analysis.
- Adverse Events were coded according to the MedDRA V6.1 classification whatever the severity level, the relationship to treatment or the possible withdrawal to study treatment.
- Treatment-emergent AEs (TEAEs) were defined as AEs that developed or worsened during the treatment period and until 14 days after the last dose of study medication.
- Deaths and Serious Adverse Events Deaths or serious adverse events were listed and commented.
- Adverse Events leading to treatment discontinuation Patients with AE leading to treatment discontinuation were listed and commented.

✓ **evaluation of the pharmacokinetic parameters** for Kigabeq (population PK). A model was to be developed for each vigabatrin enantiomer. Influence of continuous covariates (weight, age, body surface area, creatinine clearance) was to be integrated in an allometric relation. An intermediate multivariate model including all the significant covariates could then be obtained.

✓ extent of exposure According to ICH recommendations,

✓ concomitant medication/therapy Frequency tables by treatment group were provided for all concomitant medications

✓ laboratory tests. To assess the individual subject changes, the following values were tabulated in the study population:

- Weight and vital signs (heart rate, diastolic and systolic blood pressure
- Physical examination: The frequencies of occurrence of each sign were described.
- EEG: A qualitative analysis of background rhythm, focal / generalized spikes, focal / generalized slow waves and hypsarrhythmia if present was performed.
- Evaluation of plasma taurine concentrations. Taurine plasma concentration was to be measured and a relationship between vigabatrin exposition and taurine plasma levels sought.

Sample size

50 participants were expected to be enrolled in this study to reach a sample size of at least 40 evaluable patients.

Protocol and protocol amendments

However due to recruitment difficulties, the study protocol, procedures and schedule of assessments were reviewed after recruitment of 19 patients. Several amendments were made to the study protocol: extended the number of sites from 12 to 17, extended the study period by 36 weeks. The final study duration was 140 weeks (32 months), with: - Recruitment period: 102 weeks (23.5 months).

In amendment 2, Applicant included the possibility to enroll both patients under Sabril (whatever their stability status was) and naïve patients. - Changes in anti-epileptic drugs dose within 7 days before V1 were allowed. The schedule of assessments and study visits was completely reviewed to start with Kigabeq treatment for 3 months followed by 15 days of Sabril and a 4 week-follow-up period. An optional visit V2 was added especially for naïve patients. An optional 3 month-compassionate use (renewable once) was proposed at the end of the Kigabeq treatment period. If accepted, the subject was not switching to Sabril neither doing a follow-up period.

For patients under Sabril at inclusion, EEG was performed only at V3. For naive patients, EEG was performed at V1, V2 and V3. ERG remained optional. Blood samples were reduced to 2: One blood sample at V1, for laboratory tests and taurine concentration and one blood sample at V4 for laboratory tests, PK time point and taurine concentration. Diaries were still given to patients to collect secondary endpoints related to palatability and adherence. With this new schedule of visits, since some patients were expected to ask for the compassionate-use of Kigabeq and thus not return to Sabril under the protocol, missing data from Sabril diaries were anticipated. Statistical analyses: Changes were provided in the sample size section as the sample size was not calculated but only the reflexion of feasibility concerns. The "Evaluation of the pharmacokinetic parameters for vigabatrin (population PK)" section was deleted and replaced by an analysis of the unique blood sample drawn.

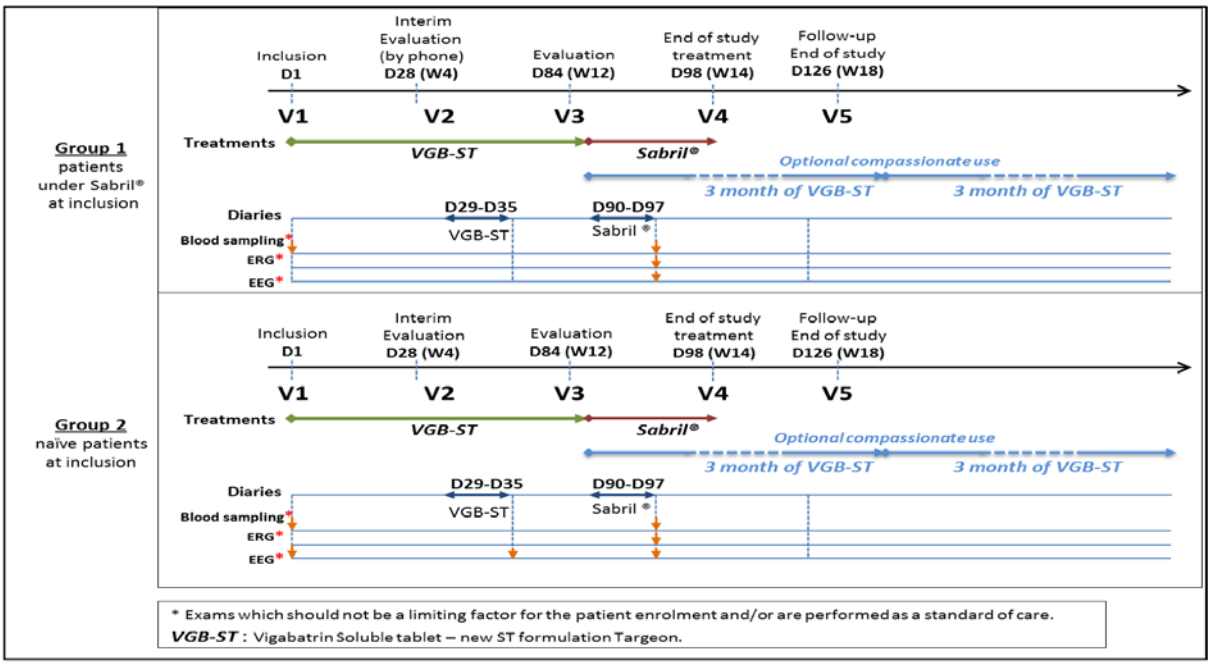


Figure 4 - Study visits and schedule of assessments after Amendment 2

Results

Thirty eight patients were enrolled in the study. Thirty six patients were analyzed. Twenty nine patients were already under Sabril at inclusion. Only seven were naive of vigabatrin.

Numbers analysed

The ITT population

Thirty eight (38) patients were enrolled in the study. Two patients were not considered for the ITT analysis: one patient, presenting a non-eligibility criterion, was withdrawn from the protocol before start of study treatment; the second patient withdrew his consent soon after V1. No data was available on primary endpoint for these two subjects. The ITT analysis was thus performed on 36 patients. For two of the ITT patients, adherence data was completely missing (the patients did not bring back the MEMS). For these patients the analysis was performed considering they had an adherence of the 1st decile value. A second analysis without replacement of missing data was performed on 34 patients with partial or complete primary endpoint. All patients with partial data for the primary endpoint were excluded from the per protocol analysis.

The PP analysis was performed on 28 patients. The primary endpoint being adherence, effective start and end date of treatment were considered to define the extent of exposure.

Demographic and other baseline characteristics

A total of 38 patients were enrolled in the study. Among the 36 patients considered for the ITT analysis, 8 (22%) were between 1 and 6 months of age, 18 (50%) were between 6 months and 2 years of age and 10 (28%) were between 2 and 6 years of age. Mean age of enrolled patients was 1.5 years (min 2.5 months – max 5.5 years). The youngest patient was aged 1 month at inclusion and the oldest 68 months (5 years and 8 months).

Twenty-seven (75%) patients had epileptic spasms and 17 (47%) focal seizures. Nine (25%) patients presented both types of seizures. Two had another type of seizures associated: generalized tonic-clonic seizures for one and myoclonic seizures for the other one. Epilepsy was classified as symptomatic in half of the patients (n=18, 50%), due to Tuberous Sclerosis in 7 of them (39%) and to another symptomatic aetiology in the other 11 (61%), and was classified as cryptogenic in the other half (n=18, 50%). At inclusion, 8 out 18 (44%) patients with cryptogenic epilepsy presented with abnormal neurological examination and 9 out of 18 patients (50%) with symptomatic epilepsy, including 6 out of 7 (86%) of those with Tuberous Sclerosis presented abnormal neurological examination. Half of the patients were seizure-free at inclusion. The eight (23.5%) and nine (26.5%) other patients had less than one and more than one seizure per day, respectively. Among the 29 patients who were under Sabril at inclusion, all but one were considered stabilized under Sabril. The patient not considered stabilized under Sabril had variation in its vigabatrin dose prescribed during the study.

The other patients (n=7) were naive of vigabatrin treatment at inclusion. Twenty-four patients had already received another anti-epileptic drug before inclusion: benzodiazepines for 11 of them (30%), valproic acid for 8 (22%), and topiramate for 7 (19%). Hydrocortisone had been used in 7 (19%) patients.

Outcomes and estimation

Analysis of adherence

The mean adherence (95% confidence interval) under Kigabeq was 61% (47% -79%), as a result of the ITT analysis of the primary endpoint. The analysis of sensibility resulted in an adherence of 64% (48%-83%).

Table 8 - Mean adherence of Kigabeq by MEMS (ITT population)

	N	Missing	Lower Limit	Mean	Upper Limit
TOTAL	36				
Primary endpoint - MEMs adherence (ITT population)	34	2	0.47	0.61	0.79

The median adherence (inter-quartile range) assessed by MEMs was 93% (59%-100%).

Table 9 - Median adherence of Kigabeq by MEMS (ITT population)

	N	Missing	Min	Q1	Median	Q3	Max
TOTAL	36						
Primary endpoint - MEMs adherence (ITT population)	34	2	0.04	0.59	0.93	1.00	1.03

When calculated on the PP population, the mean adherence (95% CI) to treatment is 65 (47-89) %.

Table 10 - Mean adherence of Kigabeq by MEMS (PP population)

	N	Missing	Lower Limit	Mean	Upper Limit
TOTAL	28				
Primary endpoint - MEMs adherence (PP population)	28	0	0.47	0.65	0.89

The median adherence on the PP population (inter-quartile range) assessed by MEMS is 95% (60%-100%).

The secondary analysis on adherence is assessed by Kigabeq tablets and Sabril sachets accountability. Medians of adherence (inter-quartiles ranges) are 99% (95%-112%) and 93% (47%-117%) for Kigabeq and Sabril sachets respectively on the ITT population.

The classes of individual adherences observed in the SoluWest study were not normally distributed. Therefore, in real conditions, the median describes adherence better than mean, and its use seems appropriate. The mean adherence (95% confidence interval) under Kigabeq was 61% as a result of the ITT analysis but the median adherence for ITT population was 93%. In such case, an obvious question arises- what is the real cause of such a large individual variability (why did several patients have very low adherence scores).

According to the Applicant's opinion, there are several causes responsible for low individual adherence scores using the MEMS:

a) Misuse of MEMS. Some patients did not understand the functioning of the MEMS. They either left their MEMS open during the treatment period (in which case, the MEMS did not count the openings), or removed the MEMS from the bottle, or transferred the Kigabeq - tablets to another bottle.

b) Some patients did not return their MEMS (or only part of the MEMS) to the hospitals (although this was explicitly required). In this case, the individual MEMS adherence for the corresponding patient was artificially low.

c) Low individual adherence, concerned patients who had a treatment interruption (e.g. for hospitalisation) during the study: during the interruption, the MEMS were not used, so the individual adherence score was diminished.

The Applicant presented rational reasons for which low individual adherence scores using the MEMS were observed was accepted by the CHMP.

Table 11 - Median adherence of Kigabeq (-) by tablets accountability

	N	Missing	Min	Q1	Median	Q3	Max
TOTAL	36						
Adherence of VGB-ST by tablets accountability (ITT population)	35	1	0.30	0.95	0.99	1.12	2.01

Table 12 - Median adherence of Sabril by sachets accountability

	N	Missing	Min	Q1	Median	Q3	Max
TOTAL	21						
Adherence of Sabril by sachets accountability (ITT population)	19	2	0.00	0.47	0.93	1.17	1.50

The results of mean adherence assessed by Kigabeq tablets and Sabril sachets accountability are added in the detailed statistical report (version 4 dated 24/11/2017) and are also presented below.

Table 13 - Median adherence (range and quartiles) without replacing missing data

Label	N	Minimum	Lower Quartile	Median	Upper Quartile	Maximum
Adherence Kigabeq - MEMS openings	34	0.04	0.59	0.93	1.00	1.03
Adherence Kigabeq - tablets count	35	0.30	0.95	0.99	1.12	2.01
Adherence SABRIL - sachets count	19	0.00	0.47	0.93	1.17	1.50

Table 14 - Mean adherence (95% CI) without replacing missing data

Endpoint	Mean	Lower limit	Upper limit
Adherence Kigabeq - MEMS openings	0.63	0.48	0.83
Adherence Kigabeq - tablets count	0.98	0.87	1.11
Adherence SABRIL - sachets count	0.69	0.42	1.13

Note: mean (CI) calculated on the log scale and back transformation on the original scale, because the distribution is not normal.

Applicant added the results of mean adherence assessed by Kigabeq tablets and Sabril sachets accountability allowing the visualization of the potential variability in the individual adherences between Kigabeq tablets and Sabril.

Drug dose, drug concentration and relationship to response

Mean dosages of 84 mg/kg/day (min = 50 ; max = 107), 99 mg/kg/day (min = 44; max = 164) and 59 mg/kg/day (min = 33; max = 91) are observed in patients between 1 and 6 months, 6 months and 2 years and 2 years and 6 years of age respectively. Doses follow recommendations for vigabatrin administration in each subpopulation.

Table 15 - Distribution of vigabatrin dose (in mg/kg/d), per age category

Age class	N	Mean	Std Dev	Minimum	Median	Maximum
1-< 6 months	9	84.2	20.5	50.0	90.0	107.1
6 m - < 2 yrs	17	99.1	35.3	43.9	93.6	163.9
2 - 6 yrs	10	59.1	21.5	33.3	55.3	91.2

Drug concentrations

The database comprised 29 children (14 boys/15 girls) and 174 concentrations measured (87 concentrations of vigabatrin-R and 87 concentrations of vigabatrin-S). The mean (standard deviation) vigabatrin dose was 430.2 (149.8) mg. The concentration of vigabatrin-S (the active enantiomer of vigabatrin) ranged from 0.69 mg/mL to 30.41 mg/mL, reflecting the different dose regimen and the various plasma sampling times. There was no concentration below the lower limit of quantification of the method (0.2 mg/L). From the data it can be concluded that all patients were adherent to treatment and received a Kigabeq dose in the 12-hour period preceding the sampling time point.

Palatability scores, assessed by a two face-visual analogical scale, were available for 31 patients under Kigabeq and 19 patients under Sabril: - The mean palatability under Kigabeq was 1.74 +/-0.38. The mean palatability score under Sabril was 1.83 +/-0.33.

Some missing data did not account in the evaluation of the palatability because some care-givers did not fill in the questionnaires correctly and the cross was included between the two faces. Four patients did cross between the two faces every day of the week of completion and one patient crossed between the two faces, only one day. Several patients scored palatability at the same level each morning and each evening.

Table 16 - Palatability scores under Kigabeq VGB-ST

	N	Missing	Mean	Std	Min	Q1	Median	Q3	Max
TOTAL	31								
Mean VGB-ST palatability over 7 days	24	7	1.74	0.38	1.00	1.59	2.00	2.00	2.00

Table 17 - Palatability scores under Sabril

	N	Missing	Mean	Std	Min	Q1	Median	Q3	Max
TOTAL	19								
Mean Sabril® palatability over 7 days	18	1	1.83	0.33	1.00	1.71	2.00	2.00	2.00

The global satisfaction was assessed for 23 patients under Kigabeq and 19 patients under Sabril. Eighty three percent (83%) of the patients were globally satisfied with Kigabeq . Seventy-nine percent (79%) were satisfied with Sabril. Globally, patients are equally satisfied with both formulations. In terms of preference, data are available for the thirteen patients who took both formulations.

In the initial version of the protocol (V1 version of the CRF), patients were to be sampled 6 times to allow for a population PK modelling of vigabatrin to be performed. After the 2nd amendment of the protocol (V2 version of the CRF), this secondary objective was dropped and patients were sampled only once for safety evaluation (laboratory measurements).

Overall, S (+) and R (-) vigabatrin concentrations were measured on plasma samples of 32 patients (V1 and V2 versions of the CRF). 13 patients had more than 2 vigabatrin concentrations measured and 19 had only one concentration measured. All patients had detectable concentrations of the active S (+) enantiomer of vigabatrin, ranging from 0.7 to 30.4 mg/mL, which is in agreement with published data (Rey et al. 1990) and reflect the different sampling time points.

Comparing the two enantiomers, vigabatrin-S mean calculated AUC (102.2 ± 37.7mg.h/L) was lower than vigabatrin-R (133.8±49.1mg.h/L)

Taurine concentrations

At V1, the mean taurine whole blood concentration (N=24) was 100.05 (+/- 43.41) µmol/L and the mean taurine plasma concentration (N=32) was 29.55 (+/-12.44) µmol/L. There was no significant difference between patients naïve of vigabatrin and patients already exposed to vigabatrin: 88.64 and 103.85 µmol/L respectively. The mean difference between V1 and V4 was -18.51 µmol/L and was not statistically significant (p=0.308, Student test). Mean taurine plasma level was 39.61 (+/- 14.20) µmol/L at V1 (min = 18.15; max =74.92) and 29.81 (+/-8.21) µmol/L at V4 (min = 17.45; max =41.54). Mean difference between V1 and V4 was -9.80 µmol/L.

Analytical methods

Vigabatrin in plasma samples was analysed by use of a Liquid Chromatography Coupled with Tandem Mass Spectrometry (LC-MS/MS); Lower Limit of Quantitation (LLOQ) for vigabatrin was 0.2 ug/l. This allowed for quantification of the vigabatrin in the concentration range of 0.2 to 50.0 ug/L. Taurine in blood and plasma samples was analysed by use of a Liquid Chromatography with LLOQ for taurine 0.2 mg/L. This allowed for quantification of the taurine in the concentration range of 0.5 to 45.0 mg/L.

The applicant presented the validation report of quantification of the R- and S- enantiomers of vigabatrin in 100µl human plasma and the validation report of quantification of taurine in 50µl human plasma.

In the validation method of vigabatrin, the following parameters were addressed: intra-day precision and accuracy, inter-day precision and accuracy, short-term stability in plasma (at room temperature at day 1, 2, 3 and 7; at day 1, 7, 14 and one month at +4°C, -20°C and -80°C), freeze-thaw stability (3 cycles), stability of the extracts in the auto-sampler (over 5 days), carry-over and recovery. Acceptance criteria were in a plausible range. In turn, the validation method of taurine contains intra-day precision and accuracy, inter-day precision and accuracy, freeze-thaw stability (3 cycles), carry-over and matrix effect.

Calibration curve for vigabatrin quantification was prepared appropriately and allows performing quantification in the concentration range 0.2 – 50.0ug/l. The calibration curve for taurine quantification was also prepared appropriately with the concentration range from 0.2 to 50 mg/l.

According to the Applicant opinion the vigabatrin and taurine concentration evaluation in the Soluwest trial were of scientific nature only, and not meant to support the evaluation of efficacy of the new formulation, Kigabeq soluble tablets. Therefore, no information regarding incurred sample reanalysis for taurine testing was provided. That is also the reason why no full bioanalytical reports regarding vigabatrin and taurine assay in human plasma (in the Soluwest study) have been generated. Nevertheless, taurine validation report was prepared according to rules presented in the EMA guideline EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**.

Vigabatrin validation report:

The vigabatrin validation report was updated with information about the reagents and internal standard that were used.

The influence of haemolysis was investigated by comparing the VGB-R area/Internal standard and VGB-S area/Internal standard ratios obtained with 3 haemolysed blood samples spiked with a known amount of vigabatrin to the corresponding VGB-R area/Internal standard and VGB-S area/Internal standard ratios obtained with “normal” plasma sample spiked with the same amount of vigabatrin. Haemolysis was found to have no influence on the assay results.

The impact of hyperlipidemic plasma was not investigated and appears dispensable considering that infants and very young children are normally not expected to be hyperlipidemic. Besides, the use of a deuterated isotope as an internal standard is expected to balance for such a possible matrix effect from a theoretical point of view. Regarding the stability study, the values outside the acceptance criteria were individually assessed for their impact:

Condition	Sample	Bias (acceptance criteria)	Comment
RT	QC A VGB-S D0	-21 % (±20%)	Subsequent analyses at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at RT
RT	QC B VGB-S D0	-17% (±15%)	Subsequent analysis at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at RT
RT	QC C VGB-S D3	-17% (±15%)	Subsequent analysis at D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at RT

RT	QC D VGB-S D2	-16% (±15%)	Subsequent analyses at D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at RT
4°C	QC A VGB-S D0	-21 % (±20%)	Subsequent analyses at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at 4°C
4°C	QC B VGB-S D0	-17% (±15%)	Subsequent analysis at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at 4°C
-20°C	QC A VGB-S D0	-21 % (±20%)	Subsequent analyses at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at -20°C
-20°C	QC B VGB-S D0	-17% (±15%)	Subsequent analysis at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at -20°C
-80°C	QC A VGB-S D0	-21 % (±20%)	Subsequent analyses at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at -80°C
-80°C	QC B VGB-S D0	-17% (±15%)	Subsequent analysis at D1 / D2 / D3 and D7 did not show any degradation of VGB-S. This value does not impact the stability of plasma sample at -80°C

In addition to the comments provided in the table above, it is worth noting that the extent in violating the acceptance range is most often just 1% and even in the worst case not more than 2% and thus within normal variability of analytical procedures. Moreover, the criterion for incurred sample reanalysis in a BE trial allows a difference of up to 20% between initial and repeat measurement as formal confirmation of the reliability of the method. In this regard, the difference observed appears acceptable and do not significantly affect the reliability of the plasma concentrations determined.

Relative Standard Deviations (RSD) were indeed not calculated for the freeze-thaw stability study as the acceptance criteria was not the RSD but the bias between measured and theoretical concentrations.

Lastly, specificity of the bioanalytical procedure was investigated for medicines frequently prescribed in children suffering from West syndrome, i.e. valproic acid, levetiracetam, hydrocortisone, lamotrigine, topiramate, phenytoin, amoxicillin, cefotaxime, ceftazidime, imipenem, ciprofloxacine, levofloxacine, acyclovir, amlodipine, prazosine, furosemide, and paracetamol. No interference was observed with vigabatrin R and S enantiomers, as well as with their respective internal standards.

Taurine validation report:

The taurine validation report was updated with information about the reagents and internal standard that were used.

The taurine validation report was updated with a stability study performed at -80°C (storage conditions of the samples) with taurine dissolved in water as samples.

Results for 0, 1, 3, and 6 months storage are displayed in the table below:

QC A 0.2 mg/L 0.16 - 0.24					QC B 0.5 mg/L 0.425 - 0.575				
	D0	**M1**	**M3**	**M6**		**D0**	**M1**	**M3**	**M6**
	N/A	0.205	0.163	0.24		0.449	0.531	0.429	0.48
	0.183	0.211	0.19	0.201		0.467	0.505	0.428	0.463
Mean	**0.183**	**0.208**	**0.177**	**0.221**	**Mean**	**0.458**	**0.518**	**0.429**	**0.472**
Reference	**0.200**	**0.200**	**0.200**	**0.200**	**Reference**	**0.500**	**0.500**	**0.500**	**0.500**
Bias %	**-9**	**4**	**-12**	**10**	**Bias %**	**-8**	**4**	**-14**	**-6**
QC C 10 mg/L 8.5 - 11.5					**QC D 45 mg/L 38.25 - 51.75**				
	D0	**M1**	**M3**	**M6**		**D0**	**M1**	**M3**	**M6**
	9.281	8.651	8.774	9.217		41.975	39.234	40.691	41.989
	8.853	8.823	9.043	9.517		43.042	40.189	40.416	40.992
Mean	**9.067**	**8.737**	**8.909**	**9.367**	**Mean**	**42.509**	**39.712**	**40.554**	**41.491**
Reference	**10.000**	**10.000**	**10.000**	**10.000**	**Reference**	**45.000**	**45.000**	**45.000**	**45.000**
Bias %	**-9**	**-13**	**-11**	**-6**	**Bias %**	**-6**	**-12**	**-10**	**-8**

All the bias values determined met the prospectively defined acceptance criteria. Therefore, the stability of taurine in water at -80°C was validated over a 6 months period.

Incurred sample reanalysis was performed for vigabatrin quantification. In this study the scheduled total number of subject samples was 87. Incurred sample reanalysis was performed on 15 samples (17 %). As a criterion of acceptance two thirds of the repeat samples should agree within ± 20 %. In total, 100% of the repeat samples agreed within ± 20 %. Therefore, the acceptance criteria were fulfilled and incurred sample reanalysis was in accordance with the European guideline.

Patient exposure

The patient exposure calculated for the clinical study is presented below.

VGB-ST	N	Missing	Mean	Std	Min	Q1	Median	Q3	Max
TOTAL	36								
Dose VGB-ST prescribed (mg/kg/day)	35	1	84.28	33.01	33.33	54.99	83.33	103.09	163.93
Effective exposure to VGB ST (mg/kg/day)	35	1	79.51	23.18	7.00	79.00	85.00	90.00	120.00
Number of days under VGB-ST	35	1	79.06	23.91	7.00	79.00	85.00	90.00	120.00

SABRIL	N	Missing	Mean	Std	Min	Q1	Median	Q3	Max
TOTAL	21								
Effective exposure to Sabril® (mg/kg/day)	19	2	17.11	6.75	8.00	15.00	15.00	18.00	41.00
Number of days under Sabril®	19	2	16.79	6.99	8.00	15.00	15.00	18.00	41.00

Adverse events

Sixty five adverse events were notified during the study period (compassionate period not included in this report). Among these adverse events, 2 were considered as related to the study treatment by the investigators: one case of impetigo reported during the study, not requiring any action and one case of retinal toxicity found at electroretinogram examination.

For the retinal toxicity event, at the end of Kigabeq visit, the investigator and the patients discussed the consequences of stopping the treatment and not going under Sabril. It was decided to switch from Kigabeq to Sodium Valproate progressively; this was performed. Retinal toxicity is an expected adverse event with vigabatrin.

Impetigo is of infectious nature and not expected to occur under vigabatrin. This event spread over both the Kigabeq and Sabril periods. Even if the investigator considered this AE as related to study treatment, it is the opinion of the Sponsor that it is unlikely but cannot be ruled-out.

In relation to the laxative effect of mannitol, in the SoluWest study diarrhoea was reported in 2 out of 35 patients. For one patient the diarrhoea lasted for 1 day and was mild in nature. For the 2nd patient the diarrhea was also mild in nature but lasted 85 days. This may indicate that the levels of mannitol in the product can induce osmotic diarrhea.

According to the Applicant, the diarrhea was judged unrelated to the treatment by the investigator. Taking into consideration that the admitted threshold of mannitol inducing a mild laxative effect is considered to be more than 10 gr per day, equivalent to ca. 167 mg/kg/day for a 60 kg person. This amount is much higher than the quantity ingested by the patients (9.6 mg/kg/day). Therefore, according to the Applicant's opinion the amount of mannitol included in Kigabeq is too small to trigger diarrhoea.

Additionally, vigabatrin is a typical BCS class I drug which shows high aqueous solubility and fast and complete intestinal absorption. Therefore, the potential impact on absorption/efficacy is negligible. Moreover, it was observed that Kigabeq 100 mg and 500 mg soluble tablets are bioequivalent to Sabril 500 mg, granules for oral administration. The differences for PK parameters between Kigabeq and Sabril were very small and the variance was low, highlighting the fact that mannitol contained in Kigabeq has no impact on absorption/efficacy of vigabatrin.

Serious adverse event / deaths / other significant events

Twenty five Serious Adverse Events (SAE) were notified during this study from twelve different patients (31%). One death occurred during the study: a 1 year and 4 months-old girl treated with vigabatrin for infantile spasms. This SAE was declared as pneumonia related to saliva inhalation and refractory seizure increase. The investigator considered that the SAE was related to the patient's condition not to the study drug. At that time the patient was under Kigabeq (500 mg twice a day given as a solution in 2.5 mL of water), together with Zonegran, Lioresal, Depakine and Inexium. The patient died from unresolved pneumonia followed by sepsis. This case was reported to the French Health Authorities (ANSM) as a Suspected Unexpected Serious Adverse Events (SUSARs). No other SUSAR was observed in this study.

Only one SAE was considered to be possibly related to the study treatment by the clinical investigators and by the Sponsor: a 1-year-old girl, with a Tuberous Sclerosis (Bourneville syndrome). She had been under Kigabeq for CPS (400 mg twice a day) when she presented a resurgence of CPS, i.e. after 7 months of Kigabeq -ST (she was then under Kigabeq compassionate-use as allowed by the study protocol). The patient was switched to Sabril (360 mg twice a day).

Among the other 23 SAEs, 19 were considered to be possibly treatment-related:

a) Intercurrent infectious diseases, including mastoiditis (1 case); bronchiolitis (3 cases); gastroenteritis (3 cases); pneumopathy (2 cases, including the above mentioned SUSAR), febrile neutropenia due to viral infection (1 case). The Sponsor considered these SAEs unlikely to be treatment-related, in agreement with the investigator's position, but preferred to list them as possibly related since it was extremely difficult to positively rule-out the drug-SAE relationship. However, it should be emphasized here that infectious diseases are very common in the infant population and that vigabatrin is not known to have an immuno-modulating effect, which could have an effect on the infection incidence or severity.

b) Spasms resurgence or poor spasms control necessitating a drug regimen adjustment (8 cases). As indicated in Sabril SmPC, spasms resurgence or poor spasms control may be observed with any anti-epileptic treatment especially in difficult to treat forms of epilepsy like IS and pharmacoresistant CPS. Improvement can be observed upon anti-epileptic regimen adjustment. These SAE are described as treatment-related and expected.

c) Constipation (2 cases). Constipation is not listed in the undesirable effects of the Sabril SmPC, however, the drug-SAE relationship cannot be ruled-out.

Two Development Safety Update Reports (DSUR) were prepared: the first one on June 5th, 2015 covering the 1-year period from April 30th, 2014 to April 29th, 2015, the second one on May 25th, 2016 covering the 2-year period from April 30th, 2014 to April 29th, 2016. No clinical trial suspension or specific protocol modification due to lack of efficacy or safety reasons were taken.

Laboratory findings

Five patients presented low bicarbonates values at inclusion and during the study. Three of them, with another symptomatic aetiology, one with cryptogenic IS and one with Tuberous sclerosis.

Two of these five patients presented a lactacidemia, one had a suspicion of mitochondrial disease and another one was under topiramate, which could explain this acidosis.

Low bicarbonate values are considered unrelated to the study treatment and due to underlying conditions. Neurological evaluations at inclusion and after Kigabeq: Twenty abnormal examinations were found, representing 17 (53%) patients at inclusion. Among them, 6 (35%) had a Tuberous sclerosis etiology, 8 (47%) had a crytogenic etiology, 3 (18%) were classified as other symptomatic. These findings were expected in this population.

The number of measurements of taurine concentration in V1 for the whole blood (N = 24) and plasma (N = 32) was different. According to the Applicant's opinion several deviations with regards to the accountability of blood samples were recorded. It appears that 8 blood samples were not shipped to the central lab. The reason for this deviation is unknown but originates from the clinical center. It is possible that the personnel at clinical center misunderstood that both plasma and blood samples had to be shipped.

It is also noted that the applicant has not discussed the clinical relevance of taurine decrease (e.g. the correlation between the decreased taurine levels and the vigabatrin associated phototoxicity). During the procedure the applicant has been asked to discuss whether the taurine decrease findings would have any implication or require any changes for the management of patients treated with vigabatrin (e.g. taurine supplements).The applicant indicates that this point was raised and discussed with the PDCO during the evaluation of Kigabeq Paediatric Investigation Plan (PIP) in February 2014. Based on preclinical data, a causal link between vigabatrin exposition, reduced taurine levels and apparition of retinal toxicity has been postulated by a research team at "Institut de la Vision" in Paris (Jammoul et al. 2009, 2010). MAH reproduced these experiments but were unable to confirm these results.

Moreover, the Applicant`s observations have also recently been corroborated by a publication showing that there is no relationship between vigabatrin exposition and taurine plasma levels (Spelbrink *et al*. 2016). In conclusion, the Applicant believes that the possible taurine decrease in vigabatrin-exposed paediatric patients is not associated with vigabatrin retinal toxicity (no causality link). The retinal toxicity of vigabatrin is more likely due to a direct toxicity of the molecule itself, which, once processed by the GABA-transaminase, produces a chemically reactive intermediate.

Safety profile of vigabatrin (literature data)

Safety profile of vigabatrin is generally known. AEs observed for Kigabeq tablets and Sabril during the study, correspond well to those known from the literature. Additionally, based on the literature review, an Applicant has provided, in clinical overview, a very detailed description of the safety profile of vigabatrin, with particular emphasis on the population of children.

The common side effects encountered in studies include drowsiness, somnolence, nystagmus, hyperexcitability, hyperkinesia, insomnia, fever, memory impairment, depression, and confusion. Less frequently encountered are axial hypertonia, hypotonia, agitation, irritability, asthenia, laryngitis, myoclonus, diarrhoea, weight gain, and vomiting. Rare cases of psychotic reactions, mild anaemia, and decreased liver function tests. Most side-effects associated with vigabatrin use in infants are relatively benign. Vigabatrin is generally well tolerated, with adverse events similar to those experienced with other AEDs. In children with IS being on monotherapy with vigabatrin the most common treatment-related adverse events were sedation, somnolence and irritability (Walker et al, 2011). Overall, in comparison with many other AEDs, vigabatrin is well tolerated (Lerner et al, 2010).

However, one prominent vigabatrin-specific side effect has been reported: vigabatrin-induced peripheral visual field damage (VFD) (Willmore et al, 2009). VFD is retinal toxicity leading to visual field constriction. Reports of visual field deficits have appeared in the literature since 1997 (Lerner et al, 2010). Long-term observational studies have subsequently confirmed that its use is associated with asymptomatic visual field constriction (Hemming et al, 2013). Several studies have confirmed the high prevalence of VFDs (up to 30–40%) and the lack of evidence for significant progression or resolution of these defects on cessation of the drug (Best and Acheson, 2005). The prevalence of vigabatrin-associated field defects seems to be lower in children. There is particular concern that the increased risk of the VFDs will outweigh the benefit of the drug in patients who could be controlled with other AEDs. Vigabatrin should currently be used only in combination with other AEDs for patients with resistant partial epilepsy when all other appropriate drug combinations have proved inadequate or have not been tolerated. Available data suggests that VFDs are irreversible. If a visual field constriction is observed during follow-up, consideration should be given to gradual discontinuation of vigabatrin. If the decision to continue treatment is made, consideration should be given to more frequent follow-up (perimetry) in order to detect progression or sight threatening defects. Vigabatrin should not be used concomitantly with other retinotoxic drugs (SmPC Sabril 500 mg, 2016).

Neurological and psychiatric conditions; the most commonly reported side-effects in vigabatrin studies included psychomotor agitation, hyperexcitability and axial hypertonia. Although the behavioral and cognitive effects of AEDs are less than the total of other factors in epilepsy, AEDs are of special concern because they are the major therapeutic modality for seizures. Vigabatrin develops, in some patients (less than 5%), headache, dizziness, nervousness, depression, memory disturbances, speech disorder, aggression, vertigo, vision abnormalities, confusion, insomnia and impaired concentration (Sherif et al, 2015). The side effects were transitory, and no one was reported to continue after the cessation of the vigabatrin treatment (Wheless et al, 2007, Guberman, 1996).

The incidence of depression and psychosis, but not other psychiatric adverse events, occurs at a greater rate with vigabatrin than placebo. Vigabatrin use in treatment-refractory focal epilepsy is associated with increased occurrence of behavioral problems, depression and of psychosis, although the frequency of psychosis is apparently lower than previously reported (Schmitz et al, 2006). The cases of psychosis were generally transient and responded to reduction or discontinuation of vigabatrin or to neuroleptic treatment. Serious depression, defined as discontinued from the study, hospitalised, or suicide attempt, or coded as psychotic depression.

Suicidal ideation and behaviour; as worsening of depression, suicidal thoughts or behaviour, and unusual changes in mood or behavior have been reported in patients treated with antiepileptic agents including vigabatrin, patients should be monitored for signs of behavioural changes and caregivers should be advised to seek medical advice immediately if they suspect such changes (Cruz et al, 2010).

Rare reports of encephalopathic symptoms such as marked sedation, stupor and confusion in association with non-specific slow wave activity on electroencephalogram have been described soon after the initiation of vigabatrin treatment. Risk factors for the development of these reactions include higher than recommended starting dose, faster dose escalation at higher steps than recommended and renal failure. These events have been reversible following dose reduction or discontinuation of vigabatrin (SmPC Sabril 500 mg, 2016).

Vigabatrin is associated with MRI changes in the basal ganglia. These changes do not appear to be directly related to movement disorders (Fong et al, 2013). Changes consistent with reversible cytotoxic oedema have been noted in infants. The relationship between high vigabatrin dosages and vigabatrin-associated brain abnormalities (VABAM) on MRI was recently confirmed in a retrospective analysis of 507 brain MRI studies among 257 patients with IS. Vigabatrin treatment was documented in 143 children, with detailed exposure data available for 104, of whom 45 had at least one MRI study during vigabatrin treatment.

In 2009 the MHRA produced a public assessment report looking not only at the issue of vigabatrin use and brain MRI abnormalities but also at a possible association with movement disorders in infancy. The report detailed that there had been 18 reports of movement disorders identified in clinical trials with vigabatrin and that there had been 58 worldwide reports of movement disorders identified after vigabatrin was licensed and marketed. These movement disorders occurred in individuals of all ages and were of multiple different types. The report provided no evidence that the MRI changes were linked to the movement disorders. The benefit/risk of vigabatrin should be evaluated on an individual patient basis. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment (SmPC Sabril 500 mg, 2016).

Although generally effective, various AEDs have been reported on occasion to increase seizure frequency, result in seizure relapse, or elicit new types of seizures. Some seizure types and epilepsy syndromes appear more prone than others to exacerbation by a given drug. Vigabatrin is rarely associated with seizure worsening, and then mainly in patients with resistant generalised epilepsies (Lortie et al, 1993). As with the other AEDs, a gradual dose reduction is recommended when vigabatrin is discontinued (Cruz et al, 2010). If a patient is to be withdrawn from vigabatrin treatment, it is recommended that this is done by gradual dose reduction over a 2- to 4-week period (SmPC Sabril 500 mg, 2016). A number of clinical studies has shown that vigabatrin has a reliable anticonvulsant effect in double-blind, placebo-controlled trials of patients with chronic drug resistant epilepsy but to be used with care in patients with severe epilepsy especially in the presence of previous history of psychosis (Sherif et al, 2015).

Vigabatrin has demonstrated few cognitive adverse events when compared with placebo in double-blind studies and fewer adverse effects than carbamazepine in a small, open-label, randomized, parallel-group study. Vigabatrin had no detrimental effects on cognitive functions at 12 months, and memory retrieval

and mental flexibility improved significantly. Other studies reported improved cognition in children and in 66% of patients with epilepsy and psychosis. Improvements include better episodic memory, semantic memory and flexibility of mental processing in adolescents and adults and decreased arithmetic response time (Eddy et al, 2011).

Blood and lymphatic system disorders: Anaemia is one of the most feared idiosyncratric complications of the AED treatment. Anaemia with a moderate decrease in haemoglobin is a common adverse event associated with vigabatrin treatment (Livingston et al, 1989; SmPC Sabril 500 mg, 2016).

Gastrointestinal disorders, nausea, vomiting and abdominal pain are common adverse events associated with vigabatrin treatment (SmPC Sabril 500 mg, 2016; Turanli et al, 2005).

Hepatobiliary disorders; hepatitis is a very rare event associated with vigabatrin treatment (SmPC Sabril 500 mg, 2016). Skin and subcutaneous tissue disorders; Rash is an uncommon adverse event described in adults as well as in children treated with vigabatrin. Similarly, angioedema and urticarial are rare adverse events associated with vigabatrin treatment (Walker et al, 2014; SmPC Sabril 500 mg, 2016). Musculoskeletal and connective tissue disorders; arthralgia is a very common adverse event associated with vigabatrin treatment (SmPC Sabril 500 mg, 2016). General disorders and administration site conditions**;** fatigue is a very common adverse event and oedema and irritability are common adverse events associated with vigabatrin (SmPC Sabril 500 mg, 2016). Weight increased is a common side effect associated with the use of vigabatrin (Guberman, 1996, Sherif et al, 2015).

Contraindications/Warnings Contraindications; hypersensitivity to vigabatrin or to any of the excipients. Hyper-sensitivity syndrome, which is defined by fever, rash, lymphadenopathy, and derangement of liver function test can be seen in 1/100 to 1/1000 patients treated with AEDs (Karimzadeh and Bakrani, 2013). Special warnings and precautions for use**;** Except for the treatment of IS, vigabatrin should not be initiated as monotherapy (SmPC Sabril 500 mg, 2016).

Safety in special populations

Kigabeq is indicated in infants and children from 1 month to less than 7 years of age. Safety profile of vigabatrin is generally well known. Based on the literature review, the applicant has provided, in clinical overview, a very detailed description of the potential AEs, with particular emphasis on children.

Patients with renal impairment: Since vigabatrin is eliminated via the kidney, caution should be exercised when administering the drug to patients with creatinine clearance less than 60 ml/min. These patients should be monitored closely for undesirable effects such as sedation and confusion (Sabers and Gram, 1992; Wheless et al, 2007; SmPC Sabril 500 mg, 2016).

Safety related to drug-drug interactions and other interactions

Since vigabatrin is a drug that has been used for many years, the pharmacokinetic drug interactions for vigabatrin are well described. Based on the literature, the applicant has provided a detailed overview of the pharmacokinetic drug interactions of vigabatrin, in order to support the relevant sections of the SmPC.

Drug interactions with vigabatrin are few and modest. These drug interactions are not clinically significant and do not require dose adjustment for vigabatrin or concomitant medications. A 15 - 30% reduction in phenytoin concentration after vigabatrin initiation can occur. An increase of at least 10% in serum carbamazepine levels has been reported in 70% of patients with epilepsy who received adjunctive vigabatrin therapy; but dose adjustment is usually not necessary (Willmore et al, 2009). Phenobarbital

and valproate sodium plasma levels are decreased with the co-administration of vigabatrin but not in clinically significant amount.

Discontinuation due to adverse events

During the SoluWest study, one patient presented a sequence of AE's not related to treatment (pneumonia aspiration, acute respiratory distress syndrome as well as seizure) leading to stop the treatment.

Nine patients treated with Kigabeq temporarily discontinued drug administration due to adverse events not related to treatment. Sixty-five adverse events were notified during the SoluWest -an acceptability study period. Among these adverse events, 2 were considered as related to the study treatment by the investigators: one case of impetigo reported during the study, not requiring any action and one case of retinal toxicity. For the retinal toxicity event, at the end of Kigabeq visit it was decided to switch from Kigabeq to sodium valproate progressively. Retinal toxicity is an expected adverse event with vigabatrin.

These observations have also recently been corroborated by a publication showing that there is no relationship between vigabatrin exposition and taurine plasma levels (Spelbrink et al. 2016).

In conclusion, the Applicant believes that the possible taurine decrease in vigabatrin-exposed paediatric patients is not associated with vigabatrin retinal toxicity (no causality link). The retinal toxicity of vigabatrin is more likely due to a direct toxicity of the molecule itself, which, once processed by the GABA-transaminase, produces a chemically reactive intermediate.

2.6.8. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.6.9. Discussion on clinical safety aspects

Safety profile of vigabatrin is generally known. Vigabatrin is considered adequately safe and well tolerated in children with IS and in combination with other AEDs in patients with resistant partial epilepsy. Most adverse events are of mild to moderate severity. AEs observed for Kigabeq and Sabril during the TGO-VGB-III-01 study correspond to those known from the literature. Based on the literature review, the Applicant has provided, in clinical overview, a very detailed description of the individual AEs, with particular emphasis on the population of children. In children with IS being on monotherapy with vigabatrin the most common treatment-related adverse events were sedation, somnolence and irritability (Walker et al, 2011) Peripheral VFDs and white matter changes on MRI are the most prominent side effects. The common side effects encountered in studies include drowsiness, somnolence, nystagmus, hyperexcitability, hyperkinesia, insomnia, fever, memory impairment, depression, and confusion. Less frequently encountered are axial hypertonia, hypotonia, agitation, irritability, asthenia, laryngitis, myoclonus, diarrhoea, weight gain, and vomiting. Rare cases of psychotic reactions, mild anaemia. The benefit of using vigabatrin monotherapy in IS and add-on vigabatrin therapy in refractory partial epilepsy, when all other combinations of drugs have been found to be inappropriate or unacceptable, seems to outweigh the risks associated with vigabatrin treatment.

AE and SAE observed in Clinical Acceptability Study (TGO-VGB-III-01) were expected and fit in the AE characteristics for population with infantile spasms and pharmacoresistant focal epilepsy receiving vigabatrin. An acceptability study demonstrated that the acceptance and palatability of Kigabeq in the proposed paediatric target population was comparable to the Sabril. The mean adherence (95% confidence interval) under Kigabeq was 61% as a result of the ITT analysis but the median adherence for

ITT population was 93%. These differences between the mean and median values are suggestive of a large individual variability (several patients reporting low adherence scores). However the CHMP agreed with the applicant's justification that the misuse of the MEMS, non-returning of the MEMS and hospitalizations were reasonably explaining the low adherence scores.

No new particular safety issues were observed with the use of Kigabeq as compared to the reference product Sabril. It was indirectly confirmed by the adherence and palatability comparable to both study treatment groups.

In the SoluWest study diarrhoea was reported in 2 out of 35 patients. The rational reasoning presented by the Applicant, that the mannitol amount in Kigabeq is probably too low to induce osmotic diarrhoea or have an impact on absorption/efficacy of vigabatrin administered at therapeutic levels, has been accepted by the CHMP.

Abnormal laboratory findings (Low bicarbonate in five patients and lactacidemia in two of them) are considered unrelated to the study treatment and due to underlying conditions.

Moreover, the measurement of taurine concentrations in the Soluwest trial were exploratory in nature, and not meant to support the efficacy and safety evaluation of the new formulation, Kigabeq soluble tablets. Based on the obtained results and their limitations, it is difficult to draw a conclusion about the causal relationship between vigabatrin and taurine.

To exclude the possibility of adsorption to and to prove the compatibility of the proposed formulation of Kigabeq with materials commonly used in association with nasogastric feeding in infants and children, the applicant conducted an in vitro study. It was observed that there is no relevant adsorption of vigabatrin on nasogastric tubes made of polyurethane or silicone. Moreover, the results further demonstrate that vigabatrin is also not adsorbed on polypropylene commonly used in the course of preparation of the reconstituted liquid (cup) and in the course of administration (syringe).

2.6.10. Conclusions on clinical safety

A summary of the literature with regard to clinical data of vigabatrin was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

In addition no new particular safety issues with the use of Kigabeq as compared to the reference product Sabril were identified based on the data reported for the two clinical studies included in the dossier.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Visual Field Defect Suicidality
Important potential risks	Brain cytotoxic edema/MRI abnormalities Interaction with phenytoin
Missing information	None

Pharmacovigilance plan

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be

conducted.

No additional pharmacovigilance activities will be conducted.

Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product. No additional risk minimisation measures (RMMs) will be performed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0, dated February 2018 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

The applicant conducted a user consultation study in the target patient groups. During the procedure the applicant at CHMP's request the applicant adjusted the tabulated presentation of doses and the decimal description of doses in section 3 of the Patient Leaflet (PL) according to user test result. The applicant properly implemented the advice, therefore no further readability testing was considered necessary by the CHMP.

In the CHMP's view the results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a hybrid version of vigabatrin granules for oral solution. The reference product Sabril is indicated for treatment in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated and treatment in monotherapy of infantile spasms (West's syndrome).

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to

generate additional non-clinical pharmacology, pharmacokinetics and toxicology data and was considered acceptable by the CHMP.

The applicant has provided a detailed clinical overview which sums up the known facts concerning the efficacy and safety of vigabatrin in the treatment of Infantile Spasms regardless of underlying aetiology, in order to support relevant sections of the product information. The presented data have demonstrated that vigabatrin is efficacious and support its use of as monotherapy in IS or as add-on therapy in paediatric patients with epilepsy not satisfactorily controlled by conventional therapy. The dosage recommendations given in the product information are considered appropriate based on the review of published literature and clinical guidance.

In addition the applicant submitted the results of an acceptability study which demonstrated that the acceptance and palatability of Kigabeq in the proposed paediatric target population was comparable to Sabril's. Moreover, patients benefited from the new formulation by a better adjustment of the dose and demonstrated a tendency for a preference for the new formulation.

The safety profile of vigabatrin is generally well known. Vigabatrin is considered adequately safe and well tolerated in children with IS and in combination with other AEDs in patients with resistant partial epilepsy. Adverse events and serious adverse events observed for Kigabeq and Sabril during Soluwest study were expected and correspond to those known from literature. Most adverse events are of mild to moderate severity. No new particular safety issues were observed with the use of Kigabeq as compared to the reference product Sabril. The safety of Kigabeq was also indirectly confirmed by the comparable adherence and palatability to study treatment in both treatment groups.

From a clinical perspective the applicant's clinical overview based on information from published literature and the results of an acceptability study was considered sufficient.

The bioequivalence study forms the pivotal basis of this application with a open label, randomized, crossover, 2 periods study design. The study was conducted in 20 healthy male/female volunteers receiving either 500 mg of Kigabeq soluble tablets or Sabril granules for oral solution, as single oral administration under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the recommendations of the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

The choice of the population i.e. adult, healthy volunteers instead pediatric population with infantile spasm is considered appropriate and in line with the above mentioned guideline. The methodology related to sample size calculation and statistical evaluation of bioequivalence of two products was clearly presented and properly discussed. Choice of dose, sampling points, overall sampling time and wash-out period were considered adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Kigabeq 500 mg soluble tablets met the protocol-defined criteria for bioequivalence when compared with the Sabril 500 mg, granules for oral solution. The point estimates and their 90% confidence intervals for the parameters AUC0-t and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

In addition, the justification for requesting bio-waiver for the lower strength i.e. Kigabeq 100 mg soluble tablets was prepared according to general bio-waiver criteria as specified in the Guideline on the Investigation of Bioequivalence. Kigabeq 100 mg satisfy the conditions for bio-waiver of in vivo bioequivalence study with Kigabeq 500 mg soluble tablets: both strengths are manufactured by the same manufacturing process, the qualitative composition of both strengths is the same and both strengths

show a quantitatively proportional composition and both strengths show appropriately similar in-vitro dissolution characteristics.

A positive benefit/risk ratio can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kigabeq is favourable in the following indication:

Kigabeq is indicated in infants and children from 1 month to less than 7 years of age for:

- Treatment in monotherapy of infantile spasms (West's syndrome).
- Treatment in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy (focal onset seizures with or without secondary generalisation), that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Obligation to conduct post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0083/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.