25 February 2021
EMA/165350/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Briviact

brivaracetam

Procedure no: EMEA/H/C/003898/P46/007

Note

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

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1. Introduction

On 10 December 2020, the MAH submitted a paediatric dossier for study EP0077, completed on 15 July 2020, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

UCB is submitting the results of EP0077 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation), which requires UCB to submit information on studies conducted in the pediatric population (<18 years of age) treated with brivaracetam (BRV; BRIVIACT®). This report summarizes the results for the 1 pediatric patient who enrolled in and completed EP0077.

The clinical study report (CSR) is based on the full results of this completed postmarketing, prospective noninterventional study (NIS) of BRV, designed to collect information on the effectiveness in patients with partial-onset seizures (POS) who were treated with BRV in clinical practice after the product was marketed in the EU.

2.2. Information on the pharmaceutical formulation used in the study

Three formulations have been developed for commercial use: film-coated tablets for oral administration (10, 25, 50, 75, and 100mg), an oral solution (10mg/mL), and a solution for intravenous (IV) injection (10mg/mL). Brivaracetam film-coated tablets, oral solution, and solution for IV injection show the same area under the concentration-time curve, while the maximum plasma concentration is slightly higher after IV administration.

CHMP comment:

This report concerns a single paediatric patient. No data of relevance regarding suitability of the different pharmaceutical formulations for paediatric use can therefore be derived from this submission.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- EP0077, a postmarketing, prospective noninterventional study (NIS) of BRV, designed to collect information on the effectiveness in patients with partial-onset seizures (POS) who were treated with BRV in clinical practice after the product was marketed in the EU.

2.3.2. Clinical study EP0077

Description

The clinical study report (CSR) is based on the full results of this completed postmarketing, prospective noninterventional study (NIS) of BRV, designed to collect information on the effectiveness in patients with partial-onset seizures (POS) who were treated with BRV in clinical practice after the product was marketed in the EU.

Methods

Objective(s)

The primary study objective was to evaluate the effectiveness of BRV in patients with epilepsy with POS with or without secondary generalization in daily clinical practice. The secondary objective was to evaluate seizure control with BRV treatment.

Study design

EP0077 was a postmarketing, multinational, multicentre, prospective NIS initiated at 48 sites (43 of which enrolled patients) in 9 European countries (Denmark, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Spain, and United Kingdom), with a 12-month Observation Period.

The patients were followed as per normal clinical practice. No additional clinical diagnostic or monitoring procedures were applied. The use of an epilepsy/seizure diary, as standard clinical practice, was a requirement to enter the study. The selected questionnaires were to be used if they were part of the standard clinical practice at the sites for the management of patients with epilepsy. The choice of medical treatment was made independently by the treating physician in the regular course of practice and was not influenced by the NIS protocol.

All visits and assessments were scheduled and conducted per routine clinical practice. It was anticipated that each patient would have approximately 4 visits during their participation in this study. These visits consisted of:

- Visit 1, Baseline, Day 1: represented the first day of BRV treatment
- Visit 2, approximately 3 months after Baseline
- Visit 3, approximately 6 months after Baseline
- Visit 4, approximately 12 months after Baseline, or end of Observation Period

Study population /Sample size

It was planned to include 530 patients in the study.

One pediatric patient was enrolled in study EP0077 thereby fulfilling the requirement of reporting pediatric data as outlined in Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation).

Treatments

Brivaracetam was prescribed according to normal clinical practice and in accordance with the approved European Summary of Product Characteristics (ie, indicated as adjunctive therapy in the treatment of POS with or without secondary generalization in patients ≥16 years of age with epilepsy).

Outcomes/endpoints

The primary variable was BRV retention at 12 months (end of Observation Period). This variable was used as a measure of effectiveness.

The following secondary variables were measured:

- BRV retention at 3 and 6 months
- Absolute reduction in POS frequency (seizures per 28 days) from Baseline to 3, 6, and 12 months and end of Observation Period

- Percent reduction in POS frequency (seizures per 28 days) from Baseline to 3, 6, and 12 months and end of Observation Period
- Response based on percent reduction in POS (seizures per 28 days) at 3, 6, and 12 months and end of Observation Period (response is a reduction of ≥50%)
- Seizure freedom at 3, 6, and 12 months and end of Observation Period
- Time to first seizure after first dose of BRV

The following other variables were measured:

- Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) total and subscale (dimension) scores at 3, 6, and 12 months and end of Observation Period, and change in QOLIE-31-P scores from Baseline to 3, 6, and 12 months and end of Observation Period
- Presence of clinically meaningful change from Baseline to 3, 6, and 12 months and end of Observation Period in QOLIE-31-P
- EpiTrack® performance at 6 and 12 months
- EpiTrack change category from Baseline to 6 and 12 months and from 6 months to 12 months
- EpiTrack total score at 6 and 12 months and change from Baseline to 6 and 12 months
- EpiTrack total and individual subtest scores at 12 months and change in EpiTrack scores from Baseline to 12 months
- Clinical Global Impression of Change (CGIC) rating at 3, 6, and 12 months and end of Observation Period
- Patient's Global Impression of Change (PGIC) rating at 3, 6, and 12 months and end of Observation Period
- Change in drug load (ie, number of products, daily dose per given product, ratio of dose and defined daily dose [http://www.whocc.no/atc_ddd_index/], frequency, drug class) of antiepileptic drugs (AEDs) from Baseline to 12 months and end of Observation Period

Statistical Methods

This was an observational study with descriptive statistics.

Results

Recruitment/ Number analysed

One pediatric patient was included in the study.

Baseline data

The pediatric patient was 12.4 years old at the time of first diagnosis of epilepsy (International League Against Epilepsy seizure classification IA2 and IA3); the epilepsy etiology was autoimmune. The reported reasons for starting the patient on BRV were "behavioural side effects to current AED" and "lack of efficacy of current treatment".

The pediatric patient's 28-day adjusted Baseline all seizure and POS seizure frequencies were both 6.3 seizures; no seizures with secondary generalization were reported during the 3 months prior to the first administration of BRV. At BRV initiation, the patient was taking 3 concomitant AEDs

(eslicarbazepine, topiramate, and phenytoin) and had a total of 7 lifetime AEDs. The patient also had historical levetiracetam (LEV) use; LEV was discontinued due to insufficient efficacy. The patient did not have vagus nerve stimulation.

Efficacy results

BRV retention

The pediatric patient in EP0077 achieved BRV retention at 12 months and their last day of BRV administration was on Day 446.

Seizure frequency-related variables

Table 1 presents the seizure-related efficacy results for the pediatric patient.

Table 1 Seizure-related efficacy results for the pediatric patient

Visit [Relative day]	28-day adjusted POS frequency	Absolute reduction in POS frequency [a]	Percent reduction in POS frequency [a]	Response in POS frequency [b]	Seizure freedom [c]
Visit 1 (Baseline) [1]	6.3	-	-	-	-
Visit 2 (Month 3) [89]	3.5	2.8	44.7	No	No
Visit 3 (Month 6) [152]	4.4	1.9	29.8	No	No
Visit 4 (Month 12) [446]	0.9	5.5	86.5	Yes	No

POS=partial-onset seizure

a Reductions in POS frequency at 3, 6, and 12 months were assessed from Baseline.

b Response was defined as a ≥50% reduction from Baseline in POS frequency.

c Seizure freedom at 3, 6, and 12 months was assessed from Baseline.

The pediatric patient had a 28-day adjusted POS frequency of 6.3 seizures at Baseline, with absolute reductions in POS frequency of 2.8, 1.9, and 5.5 seizures per 28 days at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 12), respectively. The patient did not achieve seizure freedom during the study; however, the patient was a responder at Visit 4 (Month 12).

Time to first seizure

The pediatric patient had the first seizure after initiation of BRV on Day 21.

QOLIE-31-P

The pediatric patient had a lower QOLIE-31-P total score at Visit 4 (Month 12) compared with Visit 3 (Month 6) (52.2 and 84.3, respectively), indicating worsening of quality of life between these 2 visits. Since no Baseline QOLIE-31-P data were available for this patient, changes from Baseline in QOLIE-31-P scores could not be assessed; Visit 2 (Month 3) QOLIE-31-P data were also not available for this patient.

EpiTrack

No EpiTrack data were reported for the pediatric patient, as this assessment was not part of standard clinical practice at the study site attended by the patient.

Clinical Global Impression of Change

Based on the CGIC, the clinician considered the pediatric patient's condition to have very much improved at Visit 3 (Month 6) compared with Baseline, and to have been minimally worse at Visit 4 (Month 12) compared with Baseline. No Visit 2 (Month 3) CGIC data were available for this patient.

Patient's Global Impression of Change

Based on the PGIC, the pediatric patient considered their condition to have very much improved at Visit 3 (Month 6) compared with Baseline, and to have been minimally worse at Visit 4 (Month 12) compared with Baseline. No Visit 2 (Month 3) PGIC data were available for this patient.

Change in AED load

Table 2 presents the total AED load, total number of AEDs, and changes from Baseline for the paediatric patient.

Table 2 Total AED load, total number of AEDs, and changes from Baseline for the pediatric patient

Visit	Total AED load		Total number of AEDs	
	Observed result	Change from Baseline	Observed result	Change from Baseline
Visit 1 (Baseline)	3.3	-	4	-
Visit 4 (Month 12)	3.8	0.5	3	-1

AED=antiepileptic drug; BRV=brivaracetam; LEV=levetiracetam; VNS=vagus nerve stimulation

Note: Drug load per AED at the visit was calculated as: daily dose (mg)/defined daily dose.

Note: Number of AEDs included AEDs, LEV, BRV, and VNS use.

Note: AED preferred terms were collapsed into AED categories prior to counting the number of AEDs.

From Baseline to Visit 4 (Month 12), the total AED load for the pediatric patient increased from 3.3 to 3.8, while the total number of AEDs decreased from 4 to 3.

Safety results

The single pediatric patient began the study in Q3 2018 and completed the study in Q4 2019. The patient had no protocol deviations and was included in all analysis sets.

Extent of exposure

The pediatric patient's starting BRV dose was 50mg/day, with a maintenance dose of 200mg/day reached by Day 144 and a total exposure of 446 days.

Adverse events

No adverse events (AEs) or other safety relevant information were reported for the pediatric patient during her participation in the study.

2.3.3. Discussion on clinical aspects

Due to the data consisting of a single pediatric patient, results should be interpreted with caution. No change in the benefit-risk conclusion can be drawn from this single patient. Nonetheless, this patient stayed on BRV for more than 12 months and had no AEs.

This study is being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). Changes to the approved EU Product Information of BRIVIACT are not deemed necessary; thus, none are being proposed.

2.4. Rapporteur's overall conclusion and recommendation

The single paediatric patient had a treatment retention of greater than one year and a clear reduction in seizure frequency by twelve months. However, concordant reports from the treating physician and the patient show a decrease in quality of life and the global impression of change at twelve months. No adverse reactions were reported. Available data do not allow any further understanding of the discrepancy between the achieved seizure frequency reduction and the reduction in quality of life and global impression. Data from this single patient is from a regulatory perspective not informative for the overall paediatric population. It is agreed with the Applicant that no change to the approved Product Information of BRIVIACT is warranted based on the submitted paediatric data. The benefit risk balance remains unchanged and positive.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

3. Additional clarification requested

Based on the data submitted, there are no outstanding questions to the MAH.

MAH responses to Request for supplementary information