EU-RISK MANAGEMENT PLAN FOR

BRIVARACETAM

10MG, 25MG, 50MG, 75MG, AND 100MG FILM-COATED TABLETS

10MG/ML ORAL SOLUTION,

10MG/ML SOLUTION FOR INJECTION/INFUSION

VERSION 8.1

ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 8.1

Data lock point (DLP) for this RMP: 14 Jul 2020

Date of final sign off: 10 Dec 2021

Rationale for submitting an updated RMP: This RMP update is made in the frame of the application for the indication extension in the pediatric population as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients from 2 years of age with epilepsy.

Summary of significant changes in this RMP: Relevant sections of the RMP have been updated with data related to the new targeted population from 2 years to <4 years of age with epilepsy.

Details of the currently approved RMP:

Version number: 7.0

Approved with procedure: EMEA/H/C/003898/R/0025

Date of approval: 09 Oct 2020

Qualified Person for Pharmacovigilance (QPPV) name: Henri Jacoby

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorization Holder’s QPPV. The electronic signature is available on file.

Approval Signatures

Name: eu-rmp-rev2-administrative

Version: 2.0

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Document Approvals	
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LIST OF ABBREVIATIONS

AED	antiepileptic drug
ARCI	Addiction Research Center Inventory
BG	benzedrine group
BRV	brivaracetam
CBZ-E	carbamazepine-epoxide
CI	confidence interval
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia‑Suicide Severity Rating Scale
CSR	clinical study report
DDD	defined daily dose
DLP	data lock point
eCTD	electronic common technical document
EMA	European Medicines Agency
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
IQ	intelligence quotient
ISS	integrated summary of safety
LEV	levetiracetam
MedDRA®	Medical Dictionary for Regulatory Activities
PBO	placebo
POS	partial-onset seizures
QPPV	qualified person responsible for pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
SAMHSA	Substance Abuse and Mental Health Services Administration
SmPC	summary of product characteristics
SMQ	standardized Medical Dictionary for Regulatory Activities query

SUDEP	sudden unexplained death in epilepsy
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
VAS	visual analog scale

PART I: PRODUCT(S) OVERVIEW

Table 1: Product overview

Active substance	Brivaracetam
Pharmacotherapeutic group	N03AX23
Marketing Authorization Holder	UCB Pharma S.A.
Medicinal products to which this Risk Management Plan refers	1
Invented name in the European Economic Area (EEA)	Briviact® (Nubriveo in Italy)
Marketing authorization procedure	Centralized procedure
Brief description of the product	The active substance, brivaracetam, is a (2S)-2-[(4R)-2-oxo-4propyltetrahydro-1*H*-pyrrol-1-yl] butanamide.
	Brivaracetam displays high and selective affinity for synaptic vesicle protein 2A, a transmembrane glycoprotein found at presynaptic level in neurons and endocrine cells. Although the exact role of this protein remains to be elucidated, it has been shown to modulate the exocytosis of neurotransmitters.
	Important information about its composition: not applicable
Hyperlink to the Product Information	ema-combined-h-3898enannotated
Indication(s) in the EEA	**Current:** Brivaracetam is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 4 years of age with epilepsy.
	Proposed: Brivaracetam is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy.
Dosage in the EEA	**Current:** In adults, adolescents, and children ≥4 years old **Posology:** In adults The recommended starting dose is either 50mg/day or 100mg/day. The maximum dose is 200mg/day.
	In children (from 4 years of age) and adolescents weighing 50kg or more The recommended starting dose is 50mg/day. Brivaracetam may also be initiated at 100mg/day based on physician

Table 1: Product overview

	assessment of need for seizure control. The recommended maintenance dose is 100mg/day. Based on individual patient response, the dose may be adjusted between the effective dose range 50mg/day and 200mg/day. In children (from 4 years of age) and adolescents weighing less than 50kg The recommended starting dose is 1mg/kg/day. Brivaracetam may also be initiated at 2mg/kg/day based on physician assessment of need for seizure control. The recommended maintenance dose is 2mg/kg/day. Based on individual patient response, the dose may be adjusted between 1mg/kg/day and 4mg/kg/day.
	Proposed: Adults, adolescents, and children from 2 years of age. **Posology:** *Adults* The recommended starting dose is either 50mg/day or 100mg/day. The maximum dose is 200mg/day. *Children and adolescents weighing 50kg or more* The recommended starting dose is 50mg/day. Brivaracetam may also be initiated at 100mg/day based on the physician's assessment of need for seizure control. The recommended maintenance dose is 100mg/day. Based on the individual patient response, the dose may be adjusted between the effective dose range of 50mg/day and 200mg/day. *Children and adolescents weighing from 20kg to less than 50kg* The recommended starting dose is 1mg/kg/day. Brivaracetam may also be initiated at 2mg/kg/day based on the physician's assessment of need for seizure control. The recommended maintenance dose is 2mg/kg/day. Based on the individual patient response, the dose may be adjusted between 1mg/kg/day and 4mg/kg/day. *Children weighing from 10kg to less than 20kg* The recommended starting dose is 1mg/kg/day. Brivaracetam may also be initiated at 2mg/kg/day based on the physician's assessment of need for seizure control. The recommended maintenance dose is 2.5mg/kg/day. Based on the individual patient response, the dose may be adjusted in the effective dose range of 1mg/kg/day to 5mg/kg/day.
Pharmaceutical form(s) and	**Current:**

Table 1: Product overview

strength(s)	10mg, 25mg, 50mg, 75mg, and 100mg film-coated tablets, 10mg/mL oral solution, or 10mg/mL solution for injection/infusion
	Proposed: Not applicable
Is the product being subject to additional monitoring in the EU?	No

EEA=European Economic Area

PART II: SAFETY SPECIFICATION

PART II: MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1 EPILEPSY WITH PARTIAL-ONSET SEIZURES

1.1 Incidence

Epilepsy is diagnosed by fulfilling any of the following criteria: 1) two or more unprovoked seizures at least 24 hours apart, 2) one unprovoked seizure plus a 60% of greater probability of seizure recurrence during the next 10 years, or 3) epilepsy syndrome diagnosis (Fisher et al, 2014). The lifetime risk of developing epilepsy (defined as a history of epilepsy regardless of recency of seizures or use of antiseizure medication) is between 3% and 5%, with the highest incidence reported in neonates, young children, and the elderly (Banerjee et al, 2009). Overall, the incidence of epilepsy in children up to 15 years of age ranges between 30 and 397 per 100,000 person-years (Dura-Trave et al, 2008; Forsgren et al, 2005a; Cowan, 2002). The age-adjusted incidence rates of epilepsy range from 16 to 111 cases per 100,000 population (Banerjee et al, 2009).

In Europe, the age-adjusted incidence rate of epilepsy ranges from 29 to 47 per 100,000 person-years (Banerjee et al, 2009). The estimated number of new cases per year among European children and adolescents is 130,000 (incidence rate 70 per 100,000), 96,000 in adults aged 20 to 64 years (incidence rate 30 per 100,000), and 85,000 in the elderly aged 65 years and older (incidence 100 per 100,000). Approximately 20% to 30% of patients with epilepsy have more than 1 seizure per month (Forsgren et al, 2005a). In the US, the overall incidence of epilepsy ranges from 35.5 to 48 per 100,000 person-years (Theodore et al, 2006).

Based on estimates from population-based incidence studies from Europe, partial epilepsies account for 32% to 51% of new cases of epilepsy (reviewed by Banerjee et al, 2009). The incidence of partial seizures has been reported to be higher than for other seizure types with incidence rates ranging from 7.5 to 37.5 per 100,000 person-years in Western Europe (Jallon et al, 2001; Forsgren et al, 1996).

1.2 Prevalence

Epilepsy is one of the most common neurological disorders, affecting approximately 70 million people worldwide (Ngugi et al, 2010). Overall, the age-adjusted prevalence ranges from 2.7 to 41 per 1000 (Banerjee et al, 2009). In Europe, the prevalence of active epilepsy ranges from 3.2 to 7.8 per 1000 population (Forsgren et al, 2005a). It is estimated that the number of children and adolescents (individuals aged less than 20 years) in Europe with active epilepsy is 0.9 million (prevalence 4.5 to 5.0 per 1000), 1.9 million in ages 20 to 64 years (prevalence 6 per 1000), and 0.6 million in ages 65 years and older (prevalence 7 per 1000). In the US, overall prevalence ranges from 4.7 to 6.8 per 1000 population (Theodore et al, 2006).

The 2016 Global Burden of Diseases, Injuries, and Risk Factors Study estimated that there are 45.9 million (95% UI 39.9–54.6) epilepsy patients globally, with an age-standardized prevalence of 6.215 per 1000 population (95% UI: 5.401-7.370) (GBD 2016 Epilepsy Collaborators, 2019). This is consistent with findings from a recent international meta-analysis, which reported a pooled prevalence of 6.38 per 1000 (95% confidence interval [CI]: 5.57-7.30) for all epilepsy

(Fiest et al, 2017). The same study reported a pooled prevalence of 2.99 per 1000 (95% CI: 1.39-6.42) for active focal seizures (Fiest et al, 2017).

In a recent population-based study of children with epilepsy in the Norwegian Mother and Child Cohort, the authors reported a focal seizure prevalence of 271 per 100,000 for children under 14 years old. Among all children with epilepsy in this study (n=606), 27% had seizure onset before 1 year of age and another 45% had seizure onset between 1 and 4 years of age. Among all children with epilepsy in this study (n=606), 65% of those with seizure onset under 1 year of age (n=162) and 69% of those with seizure onset from 1 to 4 years of age (n=273) experienced focal seizures (Aaberg et al, 2017).

1.3 Demographics of the population in the authorized indication – age, gender, racial, and/or ethnic origin and risk factors for the disease

The burden of epilepsy is higher in developing countries than in developed countries. The median lifetime prevalence of epilepsy in developed countries is 5.8 per 1000 population (fifth to 95th percentile range: 2.7-12.4), while in developing countries it is 15.4 per 1000 person-years (fifth to 95th percentile range: 4.8-49.6) (Ngugi et al, 2010). The median prevalence of active epilepsy in developed countries is 4.9 per 1000 (fifth to 95th percentile range: 2.3-10.3), while in developing countries it is 12.7 per 1000 (fifth to 95th percentile range: 3.5-45.5) (Ngugi et al, 2010).

Limited evidence is available on occurrence of epilepsy by race or ethnicity. Higher prevalence of epilepsy was reported in African-Americans compared to Caucasians (8.2 vs. 5.4 per 1000) (Haerer et al, 1986) a lower incidence was observed among Hispanic persons (Benn et al, 2008). South Asians were reported to have a lower prevalence of active epilepsy compared to non-South Asians in a UK study (Wright et al, 2000).

For most cases of epilepsy including children and adults (approximately 55% to 75%), the cause is unknown (Cowan, 2002). For patients with epilepsy with known etiology, factors that have been attributed to cause epilepsy include cerebrovascular disease (11% to 21%), trauma (2% to 6%), tumors (4% to 7%), and infection (0 to 3%) (Olafsson et al, 2005; Oun et al, 2003; Forsgren et al, 1996).

For cases where the cause is identifiable, the etiology varies by age. In children, the most common causes of epilepsy include congenital malformations, metabolic disorders, trauma, and central nervous system (CNS) infections (Olafsson et al, 2005; Oun et al, 2003; Forsgren et al, 1996). Head trauma, CNS infections, and tumors may occur at any age and may lead to epilepsy, but tumors are more common after the age of 40 years. Cerebrovascular disease is the most common risk factor for epilepsy in people older than 60 years (Hitiris et al, 2007). The distribution of the etiological factors for epilepsy varies by geographic location (Banerjee et al, 2009). In some parts of developing countries, endemic infections such as malaria, neurocysticercosis, paragonimiasis, and toxocariasis significantly contribute to the development of epilepsy compared to other etiological factors (Singh et al, 2006; Carter et al, 2004; Senanayake and Román, 1993).

There are several factors that have been associated with an increased risk of epilepsy in children. A family history of epilepsy has been associated with an increased risk for epilepsy that ranges from 2.5- to 3-fold (Annegers et al, 1996). Children with a history of febrile and neonatal

seizures have an increased risk of epilepsy compared with those without seizures (rate ratio 5.43, 95% CI 5.19 to 5.69) (Vestergaard et al, 2007). Approximately 22% to 33.8% of children who had seizures in the newborn period will develop epilepsy (Ronen et al, 2007; Garcias Da Silva et al, 2004) and 3% to 10% of children with CNS infection or brain trauma develop epilepsy (Guerrini, 2006).

1.4 The main existing treatment options

The main goal of the treatment of epilepsy is seizure freedom. The primary treatment for epilepsy is using antiepileptic drugs (AEDs). The choice of AEDs is dependent on the age of the patient, type of seizures, presence of comorbidities, efficacy, tolerability, and ease of use of the drug; the choice is also dependent, in women, on the possibility of pregnancy, lactation, and potential teratogenic effects (Perucca and Tomson, 2011). Patients are initially started on AED monotherapy, and if they are nonresponsive, they are changed to an alternative monotherapy regimen or adjunctive therapy. The duration of each treatment trial before deciding on continuing or changing to an alternative drug depends on the occurrence of side effects and seizure frequency. According to the International League against Epilepsy task force, patients are defined as having drug-resistant epilepsy when there is failure of adequate trials of 2 tolerated, appropriately chosen, and administered AEDs (as monotherapy or in combination) to achieve seizure freedom (Kwan et al, 2010). If AEDs are not successful in controlling seizures, nonpharmacological treatments such as surgery, a ketogenic diet, or vagus nerve stimulation may be tried. Surgery is usually performed in patients with refractory epilepsy that is associated with a localized focal lesion that can be resected. The ketogenic diet is a special high-fat, low-carbohydrate diet that helps to control seizures in some people with epilepsy. The vagus nerve stimulator is an internalized implantable device that is implanted in the left upper chest under the skin and connected via electrodes to the left vagus nerve in the neck. The device is programmed to deliver intermittent stimulation every 3 to 5 minutes. It is used, for example, to manage Lennox-Gastaut syndrome in pediatric patients.

1.5 Natural history of the indicated condition in the population, including mortality and morbidity

In children who experience a first unprovoked focal or generalized tonic-clonic seizure, the cumulative risk of recurrence is 42% at 8 years follow-up, with only 3% of all recurrences occurring after 5 years (Shinnar et al, 1996). About 63% to 70% of individuals with epilepsy achieve long-term remission, and most achieve remission within 5 years of diagnosis (Kwan and Sander, 2004; MacDonald et al, 2000).

The ability to achieve remission of seizures or to discontinue antiepileptic medication varies by type of epilepsy, etiology, the presence of other neurological disorders, and initial response to treatment. The higher the number of years before entering 5-year remission, the higher was the annual risk of relapse. Those with cryptogenic or symptomatic generalized epilepsy, West syndrome, and Lennox-Gastaut syndrome had the lowest proportions of terminal remission (Sillanpää and Schmidt, 2006).

Estimates indicate that up to 10 years of life are lost for people whose epilepsy has a known cause and up to 2 years are lost for people with epilepsy from an unknown cause (Gaitatzis et al, 2004a). Studies have consistently reported higher mortality rates in children and adults with epilepsy compared with general populations. One study reported a mortality rate of 3.8 per 1000

person-years in children with epilepsy aged between 1 month and 16 years who were followed for 5 years (Callenbach et al, 2001). This was seven-fold higher (95% CI 2.4 to 11.5) than expected.

Sillanpää and Shinnar (2010) conducted a long-term mortality study in Finnish subjects in a population-based cohort of 245 children with a diagnosis of epilepsy in 1964 who were prospectively followed for 40 years. All subjects, male and female, with epilepsy due to remote symptomatic causes had a mortality rate of 11.10 deaths/1000 person-years (95% CI 8.3 to 14.9).

A meta-analysis of 21 studies that compared the mortality in patients with epilepsy to general populations reported standardized mortality ratios ranging from 1.2 to 9.3 (Shackleton et al, 2002). "A similar meta-analysis of premature mortality of epilepsy but in low- and middle-income countries reported an annual mortality rate of 19.8 (range 9.7-45.1) deaths per 1000 and standardized mortality ratio of 2.6 (range 1.3-7.2) (Levira et al, 2017). The highest mortality rates occur during the first years after seizure onset, mainly due to the underlying conditions causing the epilepsy (Neligan et al, 2010; Forsgren et al, 2005b;). However, a significant excess mortality has also been recorded, even many years after the diagnosis of epilepsy (Neligan et al, 2011). Studies of cause-specific mortality rates in patients with epilepsy have shown excess mortality from cerebrovascular disease, heart disease, and pneumonia (Neligan et al, 2011; Forsgren et al, 2005b). One of the factors contributing to the increased mortality is the occurrence of sudden unexpected death in people with epilepsy with an estimated incidence of 2 per 10,000 person-years in children with epilepsy (Donner et al, 2001). A meta-analysis of 74 studies reported a standardized mortality ratio of 3.3 (95% CI 2.8 to 3.7) comparing the mortality rate due to suicide in patients with epilepsy to the general population (Bell et al, 2009).

Mortality risk among epilepsy patients is significantly affected by demographic differences and comorbid conditions (Keezer et al, 2016). This risk was quantified in an epilepsy-specific risk adjustment comorbidity index, similar to the Charlson comorbidity index (St. Germaine-Smith et al, 2011). The epilepsy-specific comorbidity index found significant associations for age, sex, and 14 comorbid conditions: congestive heart failure, peripheral vascular disease, chronic pulmonary disease, renal disease, moderate or severe liver disease, metastatic cancer, brain tumor, solid tumor without metastasis, paraplegia and hemiplegia, aspiration pneumonia, dementia, pulmonary circulation disorders, cardiac arrhythmias, hypertension, and anoxic brain injury (St. Germaine-Smith et al, 2011). Thus, it is critical to consider an epilepsy patient's overall health status and access to care when assessing mortality risk."

1.6 Important comorbidities

Children and adults with epilepsy have a significantly higher prevalence of some psychiatric disorders, behavioral and developmental disabilities, and somatic conditions compared with the general population (Lin et al, 2012; Gaitatzis et al, 2004b; Gaitatzis et al, 2004c; Pellock, 2004).

One study found that children with epilepsy had increased prevalence of depression (8% versus 2%), anxiety (17% versus 3%), attention-deficit/hyperactivity disorder (23% versus 6%), conduct disorder (16% versus 3%), developmental delay (51% versus 3%), autism spectrum disorder (16% versus 1%), social problems (relative risk 2.16, 95% CI 1.61 to 2.90), and parental aggravation (2.19, 95% CI 1.44 to 3.32) compared with children without epilepsy (Russ et al, 2012). Studies have also found that children with uncomplicated epilepsy had lower verbal intelligence quotient (IQ) and full scale IQ than did healthy control individuals (Rantanen et al,

2010). Serious psychiatric disturbances are less common in children with epilepsy compared with adults with epilepsy (Pellock, 2004).

Comorbid conditions in adults with epilepsy have been broadly studied and are similar to those observed in children. Comorbidities occurring at a particularly high prevalence include depression, anxiety, sleep disturbances, fractures, migraine, and stroke (Swinkles et al, 2005). The prevalence of depression in epilepsy has been reported to range from 20% to 55% (TellezZenteno et al, 2007; Victoroff et al, 1994). Other psychiatric conditions that have been reportedly high in epilepsy patients include anxiety (11%) and psychoses (9%) (Hesdorffer et al, 2012; Rai et al, 2012; Gaitatzis et al, 2004c). Studies have also reported a higher prevalence of attention-deficit/hyperactivity disorder in adults with epilepsy (30% to 40%) compared to 15% in general population (Hamed, 2011). Additionally, studies have reported a high incidence of cognitive impairment including learning disability and academic underachievement in patients with epilepsy (van Blarikom et al, 2006).

The most common somatic comorbid conditions that have been reported among adults with prevalent epilepsy include fractures, ischemic heart disease, and heart failure. Studies have shown that the standardized mortality ratios for cardiovascular disease are 1.5 to 2.5 times higher in people with epilepsy than in the general population (Neligan et al, 2011). The risk of fractures in patients with epilepsy is elevated approximately 2-fold compared with the general population; the fractures result directly from seizure-induced injury or the reduction in bone mineral density associated with use of enzyme-inducing AEDs (Wirrell, 2006). Among older adults, the occurrence of either stroke or epilepsy is associated with an increased risk for the other condition (Cleary et al, 2004; Hauser et al, 1993). Studies involving adults at least 18 years of age with epilepsy have also reported sleep disturbance conditions including increased latency to sleep onset, increased number and duration of awakenings, and increased duration of sleep stages 1 and 2 (van Golde et al, 2011).

Although epilepsy does not increase the risk of cancer, patients with cancer have an increased risk of developing epileptic seizures in the course of their disease. The lifetime risk of patients with brain tumors to have epileptic seizures is 20% to 80% (van Breemen et al, 2007). The risk of having epileptic seizures is higher in patients with primary brain tumors than in those with brain metastasis. Seizures can occur in patients with cancer in the absence of CNS involvement. Even when a brain lesion is present, it may not be the cause of seizures. Other factors that cause seizures in these patients include medications, metabolic disturbances, stroke, and infection (Singh et al, 2007). Patients with Alzheimer’s disease are at increased risk for developing seizures and epilepsy. The reported lifetime prevalence rates of seizures in patients with Alzheimer’s disease ranges from 1.5% to 64% (Friedman et al, 2012).

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PART II: MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies

Key safety findings and relevance to human usage are detailed in Table 1–1

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
General safety pharmacology	
Cardiovascular findings (including potential for QT interval prolongation) The potential for cardiovascular effects of brivaracetam (BRV) was tested in vitro and in vivo. Brivaracetam did not induce significant effects on human cardiac sodium, calcium, and potassium channels up to 100µM and in canine Purkinje fibers up to 200µg/mL (0.9mM). Brivaracetam lowered blood pressure and increased heart rate at oral doses ≥50mg/kg in conscious female dogs (corresponding C_{max} of 61µg/mL at 50mg/kg). The effects were not dose-related and were not observed in males. Transient decreases in blood pressure, heart rate, and cardiac contractility were observed in anesthetized male dogs after an intravenous injection of 150mg/kg; no effects were observed at 45mg/kg (plasma levels of 131µg/mL at the end of the 10-min infusion). Prolongation of QT_c interval as observed in female dogs at an oral dose of 150mg/kg. No prolongation of QT or QT_c duration was apparent in the 2-, 4-, 13-, and 26-week repeated dose toxicity studies in the dog at any dose tested (C_{max} ranging from 23.5 to 211.8µg/mL). QT and QT_c were also unaffected in the 4- and 39-week toxicity studies in the monkey, up to 900mg/kg/day (C_{max} of 223µg/mL). It was concluded that BRV is unlikely to affect cardiac conduction, depolarization, and repolarization. Overall, the cardiovascular effects that were observed at doses ≥50mg/kg in the dog (with corresponding plasma levels at least 17-fold higher than the clinical C_{max} of 3.5µg/mL at the dose of 100mg) were not dose-related, were inconsistent between sexes, and were not observed in the repeated dose toxicity studies.	From nonclinical studies, it is concluded that BRV is unlikely to affect cardiac conduction, depolarization, and repolarization. In addition, pooled clinical data from studies of BRV (including a thorough QT study, N01233) did not detect clinically significant signals of cardiotoxicity. In conclusion, there is currently no safety concern for cardiac events.

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
Nervous system findings In a standard battery of safety pharmacology studies in rodents, the predominant effects were central nervous system (CNS)-related and key findings included transient CNS depression and decreased spontaneous locomotor activity in rats at doses ≥100mg/kg. The CNS effects were of low severity up to 300mg/kg (with corresponding C_{max} at least 30-fold the clinical C_{max} at 200mg/day). In monkeys, CNS signs (prostrate, loss of balance, clumsy movements) occurred at 900mg/kg/day (associated C_{max} 64-fold the clinical C_{max}), these effects being less apparent over time.	The relevance to human dosage is considered likely. As BRV is designed to be CNS-active, it is expected that some CNS-related signs may be observed. Pooled data from pivotal Phase 3 studies indicated that the incidences of the most frequently reported CNS-related adverse events (somnolence, fatigue, and dizziness) were higher in the BRV 50mg, 100mg, and 200mg groups than in the placebo group (Integrated Summary of Safety [ISS] Original Submission Table 5.2.1.1.1).
Toxicity	
Nephrotoxicity In repeat-dose (up to 26 weeks) oral toxicity studies in rats, hyaline droplet nephropathy was observed in males only at all dose levels.	Hyaline droplet nephropathy is known to be an adverse effect specific to male rats and is not considered of toxicological relevance for humans.
Hepatotoxicity In repeat-dose (up to 26 weeks) oral toxicity studies in dogs, there were signs of hepatotoxicity from 37.5mg/kg/day, which consisted of brown pigment (porphyrin) deposits in hepatocytes, Kupffer cells, and bile canaliculi, centrilobular fibrosis, and hyperplasia of oval cells/bile ducts, accompanied by increases in some liver enzymes as increased liver weight, single hepatocyte necrosis, inflammatory cell infiltrate, and concretions in the lumen of the gall bladder at higher dose. Based on these findings, the no observed adverse-effect level was set at 15mg/kg/day, with a corresponding $AUC_{(0-24)}$ value of 34.7µg.h/mL. This exposure corresponds to approximately 0.6-fold the exposure at a dose of 200mg/day in adult humans (56µg.h/mL). In rats, doses up to 450mg/kg/day (26-week study) or in monkeys, doses up to 900mg/kg/day (39-week study) resulted only in an adaptive response by the liver, with margins of safety of 5- to 8-fold in rats and 42-fold in monkeys.	Toxicological and mechanistic data accumulated on BRV and the structurally related compound ucb-01747-1 suggests that dog porphyria had developed as a result of combined factors. These factors include the following: • Bioactivation via oxidation of the butyramide side-chain leading to the formation of a reactive metabolite which has structural similarities with known porphyrogenic agents • Alkylation of cytochrome P450 (CYP) by this reactive metabolite resulting in N-alkylPP formation and CYP inactivation and presumably in nonlinear pharmacokinetics • Induction of heme synthesis Inhibition of ferrochelatase, the last enzyme in heme biosynthetic pathway, by N-alkylPP and CYP inactivation led to accumulation of porphyrin precursors, namely protoporphyrin. This accumulation of protoporphyrin is also accelerated by the upregulation of the heme biosynthetic pathway through CYP induction. In

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
	marked contrast to dogs, BRV data generated in humans showed no evidence of bioactivation (ie, no butyramide side-chain oxidation), CYP inactivation, nonlinear pharmacokinetics (as a result of autoinhibition), or clinically relevant CYP induction. Therefore, the induced porphyria is considered of no relevance for humans. This is supported by lack of clinically meaningful changes from baseline to the last value in the treatment period for blood chemistry parameters related to liver function tests in placebo-controlled, fixed-dose clinical Phase 3 studies (ISS Original Submission Table 6.2.2.1.1). None of the treatment-emergent adverse events were serious. Similar results were observed across the BRV program, and no clinical signal of concern has emerged.
Reproductive and developmental toxicity Brivaracetam did not affect male or female fertility in the rat. Brivaracetam has not demonstrated teratogenic potential in the rat or the rabbit. Embryotoxicity was observed in rabbits at a maternal toxic dose of BRV, with an exposure level 8-fold the clinical AUC exposure at the maximum recommended dose. In rats, BRV was shown to readily cross the placenta and to be excreted in milk of lactating rats with concentrations similar to maternal plasma levels.	The relevance to human usage is unknown as BRV has not been studied in pregnant women, but there has been no suggestion of reproductive or developmental toxicity to date.
Developmental toxicity (juvenile animals) In a juvenile toxicity study in rats, the highest dose tested (600mg/kg/day) was considered to induce developmental adverse effects with increased mortality, clinical signs, and decreased mean body weights essentially in preweaning pups. At this high dose level, a lower mean brain weight was observed mainly on postnatal Day (PND) 71 in both sexes. The no-observed-adverse-effect level was considered to be 300mg/kg/day in males and 150mg/kg/day in females. The corresponding $AUC_{(0-24)}$ (239 to 253µg.h/mL) gives an exposure	The lower absolute brain weight observed in rats only at 600mg/kg/day, which was not associated with any effects on neuropathology, was considered to result from the generalized toxicity and diminished bodyweight gain that began from PND4. It was shown that at this age relatively high exposures of BRV were achieved compared to later (>PND21) time periods, and the etiology of this finding is considered to be related to this very early “acute” toxicity resulting from these high exposures. The relevance to human usage is currently unknown. In line with the recommendation from the Pediatric Committee, head circumference is

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
ratio of 4 compared with the anticipated exposure at 4mg/kg/day in children. In juvenile dogs, and consistent with adult animals, the target organ was the liver. There were no adverse effects on growth (including femur length), bone density or strength (both femur of lumber vertebrae), and brain (mean weight, length, and width) and on neurobehavioral assessments and neuropathology (CNS and peripheral nervous system) evaluation.	monitored in the BRV pediatric studies to monitor the potential impact of brain size. In addition, height and body weight are measured at each visit to monitor the growth of children. Neurodevelopmental maturation is also monitored using validated and reliable scales depending on the age of the children and mental/intellectual status. As of 14 Jul 2020, the effect of BRV on behavior and cognition in pediatric subjects as assessed by the Achenbach child behavior checklist (CBCL)/1 and half-5 and CBCL/6-18 and Behavior Rating Inventory of Executive Function (BRIEF)/BRIEF-Preschool version questionnaires showed small improvements (decreases) from baseline for most subscale scores, but due to the large variability in the results, interpretation of the results is difficult. There did not appear to be a worsening over time with BRV treatment.
Genotoxicity and carcinogenicity In 2-year carcinogenicity studies, a modest increase in the incidence of hepatocellular tumors was observed in male mice. Brivaracetam did not possess any oncogenic potential in rats or in female mice, and BRV is neither mutagenic nor clastogenic when evaluated in vitro in bacterial and mammalian cells and in vivo in rats. These findings in male mice correlated with the presence of hypertrophic changes in the liver and significant induction in drug metabolizing enzymes (predominantly in male mice) and are consistent with a nongenotoxic phenobarbital-like effect of treatment which is known to be specific to rodents. Lack of genotoxicity of BRV was confirmed by the absence of BRV induced mutations in the liver and bone marrow in a Muta™ mouse assay. The findings in male mice are, thus, not considered as a cause of concern.	Data from the carcinogenicity studies along with genotoxicity data did not demonstrate evidence for potential tumorigenic risk for humans.
Other toxicity-related information or data Abuse and dependence liability: Brivaracetam does not demonstrate any significant abuse or dependence liability. Brivaracetam tested up to 320mg/kg/day did not demonstrate subjective effects similar to chlordiazepoxide, an	A human abuse potential study in recreational drug users demonstrated some similarities in subjective abuse potential to alprazolam but also differences on a number of endpoints, and the overall profile was more similar to the unscheduled structurally related antiepileptic drug (AED) levetiracetam. In addition, the similarities

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
anticonvulsant and anxiolytic agent with known abuse properties, as shown by lack of full substitution to chlordiazepoxide. There was a lack of any withdrawal signs following 30 days treatment of up to 450mg/kg/day. Brivaracetam at doses up to 10mg/kg/infusion did not show reinforcing properties in rats conditioned to self-administer cocaine.	were primarily seen at a very high dose of BRV (10 times the highest available tablet strength). These data are consistent with that of Class V AEDs, such as ezogabine, lacosamide, and pregabalin, which also showed some similarities to their Class IV benzodiazepine comparators in the human abuse potential study but also some differences. The absence of signs for abuse or dependence potential in targeted nonclinical studies supports these conclusions.
Mechanisms for drug interactions No major risks for drug-drug interactions were identified in vitro. The only findings were inhibition of CYP2C19 and induction of CYP3A4 and CYP2B6. They were generally observed at high in vitro concentrations (ie, >10-fold the C_{max} after oral administration at 100mg twice daily in humans). Brivaracetam was found to inhibit epoxide hydrolase, with a half maximal inhibitory concentration (IC50) varying with the test system (from 8µM in human hepatocytes to 108µM in human liver microsomes). In addition, BRV and its main circulating metabolites had no clinically relevant in vitro inhibitory effect on any of the tested transporters (eg, P-glycoprotein , breast cancer resistance protein). The exception is organic anion transporter 3, which is inhibited by BRV in vitro, with a half maximal inhibitory concentration 42-fold higher than the C_{max} at the highest clinical dose. Brivaracetam is eliminated by several metabolic pathways involving amidase (E.C.3.5.1.4), CYP2C19, and CYP2C9. Overall, data demonstrated that BRV is not a substrate of any tested drug transporters. In addition, in vitro assays showed that BRV disposition should not be significantly affected by cannabidiol.	In vitro studies suggest a low risk of drug-drug interactions with coadministered drugs that are substrate of CYPs, epoxide hydrolase, and active transporters in vivo. The extent of metabolism, various enzymes involved, and lack of active transport make BRV unlikely to give significant drug interactions (as victim drug) when coadministered with metabolizing enzyme or transporter inhibitors. In subjects receiving BRV for adjunctive treatment of partial-onset seizures, no dose adjustment is required when BRV 50 to 200mg/day is added to carbamazepine, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, and zonisamide. In controlled studies, carbamazepine epoxide is increased from 37% to 98% by BRV 50 to 200mg/day, respectively. In formal drug-drug interaction studies, BRV was devoid of clinically relevant interactions with topiramate, lamotrigine, gemfibrozil, midazolam, ethinylestradiol, and levonorgestrel (combined oral contraceptive). The oral contraceptive did not modify the plasma concentration of BRV. The induction of CYP2B6 has not been investigated in vivo and BRV may decrease plasma concentrations of medical products metabolised by CYP2B6 (eg, efavirenz). Enzyme-inducing AEDs carbamazepine, phenytoin, and phenobarbital decrease BRV concentrations by 26%, 21%, and 19%, respectively, which does not require dose

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
	adjustments. Rifampicin reduces BRV concentrations by 45%. Physicians should consider increasing the BRV dose in patients starting treatment with rifampicin. The plasma concentration of BRV is slightly increased in poor metabolizers of CYP2C19 (carriers of mutations *2 or *3 resulting in nonfunctional isoenzyme), which does not require dose adjustments.

AED=antiepileptic drug; BRIEF=behavior rating inventory of executive function; BRV=brivaracetam; CBCL=child behavior checklist; CNS=central nervous system; CYP=cytochrome P450; ISS=integrated summary of safety; PND=postnatal day

PART II: MODULE SIII: CLINICAL TRIAL EXPOSURE

1 CLINICAL TRIAL EXPOSURE

Cumulative study participant exposure from ongoing and completed clinical studies is presented by duration of exposure in Table 1–1 , by age and gender in Table 1–2 and in Table 1–4 , and by racial group in Table 1–5. Each of these tables is also provided for blinded exposure in the ongoing Study EP0083 and labeled as Table 1-Xa. Finally, cumulative study participant exposure by dose is presented for each indication in Table 1–6 to Table 1–12. For completed studies, the estimates are based on actual exposure data. For the blinded exposure tables, estimates are based on blinded exposure as of 14 Jul 2020.

Table 1–1: Duration of exposure to BRV

Indication	Number of study participants	Subject-years of exposure
Cumulative for all indications		
<1 month	1071	30.281
1 to <3 months	338	47.669
3 to <6 months	305	108.238
6 to <12 months	388	275.496
12 to <24 months	384	540.862
24 to <36 months	299	742.979
36 to <60 months	517	2008.857
60 to <96 months	356	2229.415
96 to <108 months	223	1861.933
108 to <120 months	95	869.758
120 to <132 months	55	576.356
≥132 months	73	832.298
Total	**4104**	**10,124.142**
Phase 1		
<1 month	793	18.026
1 to <3 months	106	11.852
3 to <6 months	7	1.802
6 to <12 months	0	Not applicable (NA)
12 to <24 months	0	NA
24 to <36 months	0	NA
36 to <60 months	0	NA
60 to <90 months	0	NA

Table 1–1: Duration of exposure to BRV

Indication	Number of study participants	Subject-years of exposure
90 to <108 months	0	NA
108 to <120 months	0	NA
120 to <132 months	0	NA
≥132 months	0	NA
Total	**906**	**31.680**
Partial-onset seizure		
<1 month	112	4.126
1 to <3 months	198	31.962
3 to <6 months	268	95.992
6 to <12 months	351	248.594
12 to <24 months	349	492.329
24 to <36 months	285	708.925
36 to <60 months	490	1901.144
60 to <96 months	328	2049.550
96 to <108 months	208	1736.137
108 to <120 months	74	674.708
120 to <132 months	49	515.075
≥132 months	64	726.294
Total	**2776**	**9184.835**
Unverricht-Lundborg disease		
<1 month	3	0.189
1 to <3 months	3	0.539
3 to <6 months	9	2.938
6 to <12 months	17	12.548
12 to <24 months	11	14.847
24 to <36 months	3	7.012
36 to <60 months	11	42.467
60 to <96 months	7	40.572
96 to <108 months	4	34.051
108 to <120 months	19	176.873
120 to <132 months	6	61.281

Table 1–1: Duration of exposure to BRV

Indication	Number of study participants	Subject-years of exposure
≥132 months	9	106.004
Total	**102**	**499.247**
Postherpetic neuralgia		
<1 month	83	6.012
1 to <3 months	19	1.648
3 to <6 months	0	NA
6 to <12 months	0	NA
12 to <24 months	0	NA
24 to <36 months	0	NA
36 to <60 months	0	NA
60 to <96 months	0	NA
96 to <108 months	0	NA
108 to <120 months	0	NA
120 to <132 months	0	NA
≥132 months	0	NA
Total	**102**	**7.661**
Essential tremor		
<1 month	44	1.744
1 to <3 months	0	NA
3 to <6 months	0	NA
6 to <12 months	0	NA
12 to <24 months	0	NA
24 to <36 months	0	NA
36 to <60 months	0	NA
60 to <96 months	0	NA
96 to <108 months	0	NA
108 to <120 months	0	NA
120 to <132 months	0	NA
≥132 months	0	NA
Total	**44**	**1.744**
Other seizure types		

Table 1–1: Duration of exposure to BRV

Indication	Number of study participants	Subject-years of exposure
<1 month	36	0.183
1 to <3 months	12	1.667
3 to <6 months	21	7.507
6 to <12 months	20	14.355
12 to <24 months	24	33.687
24 to <36 months	11	27.042
36 to <60 months	16	65.320
60 to <96 months	21	139.294
96 to <108 months	11	91.745
108 to <120 months	2	18.177
120 to <132 months	0	NA
≥132 months	0	NA
Total	**174**	**398.976**

BRV=brivaracetam; NA=not applicable

Table 1–1a: Duration of blinded exposure (EP0083 only)

Indication	Number of study participants	Subject-years of blinded exposure
Partial-onset seizure		
<1 month	5	0.274
1 to <3 months	14	2.489
3 to <6 months	130	39.696
6 to <12 months	41	26.352
12 to <24 months	36	55.540
24 to <36 months	7	15.310
36 to <60 months	0	NA
60 to <96 months	0	NA
96 to <108 months	0	NA
108 to <120 months	0	NA
120 to <132 months	0	NA
≥132 months	0	NA

Table 1–1a: Duration of blinded exposure (EP0083 only)

Indication	Number of study participants	Subject-years of blinded exposure
Total	**233**	**139.661**

NA=not applicable

Table 1–2: Cumulative study participant exposure to BRV by age group and gender

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Cumulative for all indications						
Preterm newborn infants	0	0	0	Not applicable (NA)	NA	NA
Term newborn infants (0 to 27 days)	[redacted]	[redacted]	[redacted]	0.003	0.005	0.008
Infants and toddlers (28 days to 23 months)	19	16	35	43.652	52.476	96.129
Children (2 to 11 years)	89	70	159	303.688	196.115	499.803
Adolescents (12 to 17 years)	71	67	138	230.834	194.270	425.103
Adults (18 to 64 years)	1976	1641	3617	4905.741	4011.321	8917.062
Elderly people						
65 to 74 years	56	61	117	72.298	105.103	177.402
75 to 84 years	18	18	36	6.990	1.645	8.635
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	[redacted]	[redacted]	**5563.206**	**4560.936**	**10,124.142**
Phase 1						
Preterm newborn infants	0	0	0	NA	NA	NA
Term newborn infants (0 to 27 days)	0	0	0	NA	NA	NA
Infants and toddlers (28 days to 23 months)	0	0	0	NA	NA	NA
Children (2 to 11 years)	0	0	0	NA	NA	NA
Adolescents (12 to 17 years)	0	0	0	NA	NA	NA
Adults (18 to 64 years)	606	280	886	18.459	12.690	31.149

Table 1–2: Cumulative study participant exposure to BRV by age group and gender

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Elderly people						
65 to 74 years	[redacted]	[redacted]	[redacted]	0.175	0.164	0.339
75 to 84 years	[redacted]	[redacted]	[redacted]	0.093	0.099	0.192
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	[redacted]	[redacted]	**18.727**	**12.953**	**31.680**
Partial-onset seizure						
Preterm newborn infants	0	0	0	NA	NA	NA
Term newborn infants (0 to 27 days)	0	0	0	NA	NA	NA
Infants and toddlers (28 days to 23 months)	12	[redacted]	[redacted]	31.483	19.017	50.500
Children (2 to 11 years)	67	53	120	243.001	153.706	396.706
Adolescents (12 to 17 years)	64	58	122	212.474	161.221	373.695
Adults (18 to 64 years)	1240	1226	2466	4520.997	3662.464	8183.461
Elderly people						
65 to 74 years	21	26	47	70.464	103.181	173.645
75 to 84 years	[redacted]	[redacted]	[redacted]	6.070	0.758	6.828
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	[redacted]	[redacted]	**5084.487**	**4100.348**	**9184.835**
Unverricht-Lundborg disease						
Preterm newborn infants	0	0	0	NA	NA	NA
Term newborn infants (0 to 27 days)	0	0	0	NA	NA	NA
Infants and toddlers (28 days to 23 months)	0	0	0	NA	NA	NA
Children (2 to 11 years)	0	0	0	NA	NA	NA
Adolescents (12 to 17 years)	[redacted]	[redacted]	[redacted]	1.172	12.214	13.385
Adults (18 to 64 years)	49	50	99	237.314	248.548	485.862
Elderly people						
65 to 74 years	0	0	0	NA	NA	NA

Table 1–2: Cumulative study participant exposure to BRV by age group and gender

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
75 to 84 years	0	0	0	NA	NA	NA
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	[redacted]	[redacted]	**238.486**	**260.761**	**499.247**
Postherpetic neuralgia						
Preterm newborn infants	0	0	0	NA	NA	NA
Term newborn infants (0 to 27 days)	0	0	0	NA	NA	NA
Infants and toddlers (28 days to 23 months)	0	0	0	NA	NA	NA
Children (2 to 11 years)	0	0	0	NA	NA	NA
Adolescents (12 to 17 years)	0	0	0	NA	NA	NA
Adults (18 to 64 years)	17	28	45	1.363	2.133	3.496
Elderly people						
65 to 74 years	17	19	36	1.328	1.380	2.708
75 to 84 years	[redacted]	11	21	0.706	0.750	1.457
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	**58**	**102**	**3.398**	**4.263**	**7.661**
Essential tremor						
Preterm newborn infants	0	0	0	NA	NA	NA
Term newborn infants (0 to 27 days)	0	0	0	NA	NA	NA
Infants and toddlers (28 days to 23 months)	0	0	0	NA	NA	NA
Children (2 to 11 years)	0	0	0	NA	NA	NA
Adolescents (12 to 17 years)	0	0	0	NA	NA	NA
Adults (18 to 64 years)	15	[redacted]	22	0.600	0.282	0.882
Elderly people						
65 to 74 years	[redacted]	[redacted]	18	0.329	0.375	0.704
75 to 84 years	[redacted]	[redacted]	[redacted]	0.120	0.038	0.159
≥85 years	0	0	0	NA	NA	NA

Table 1–2: Cumulative study participant exposure to BRV by age group and gender

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Total	[redacted]	[redacted]	[redacted]	**1.049**	**0.695**	**1.744**
Other seizure types						
Preterm newborn infants	0	0	0	NA	NA	NA
Term newborn infants (0 to 27 days)	[redacted]	[redacted]	[redacted]	0.003	0.005	0.008
Infants and toddlers (28 days to 23 months)	[redacted]	12	19	12.170	33.459	45.629
Children (2 to 11 years)	22	17	39	60.687	42.409	103.097
Adolescents (12 to 17 years)	[redacted]	[redacted]	13	17.188	20.835	38.023
Adults (18 to 64 years)	49	50	99	127.009	85.205	212.214
Elderly people						
65 to 74 years	[redacted]	[redacted]	[redacted]	0.003	0.003	0.005
75 to 84 years	0	0	0	NA	NA	NA
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	[redacted]	[redacted]	**217.060**	**181.916**	**398.976**

BRV= brivaracetam; NA=not applicable

Table 1–3a: Cumulative study participant blinded exposure by age group and gender (EP0083 only)

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Cumulative for all indications						
Preterm newborn infants	0	0	0	Not applicable (NA)	NA	NA
Term newborn infants (0 to 27 days)	0	0	0	NA	NA	NA
Infants and toddlers (28 days to 23 months)	0	0	0	NA	NA	NA
Children (2 to 11 years)	0	0	0	NA	NA	NA
Adolescents (12 to 17 years)	[redacted]	[redacted]	11	1.572	1.834	3.406

Table 1–3a: Cumulative study participant blinded exposure by age group and gender (EP0083 only)

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Adults (18 to 64 years)	98	120	218	63.417	70.297	133.714
Elderly people						
65 to 74 years	[redacted]	[redacted]	[redacted]	0.359	0.271	0.630
75 to 84 years	[redacted]	0	[redacted]	1.911	NA	1.911
≥85 years	0	0	0	NA	NA	NA
Total	[redacted]	[redacted]	[redacted]	**67.258**	**72.402**	**139.661**

NA=not applicable

Table 1–4: Cumulative study participant exposure to BRV by grouped age and gender

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Cumulative for all indications						
<4 years	26	21	47	66.809	62.710	129.520
4 to <16 years	116	99	215	364.047	253.700	617.747
≥16 years	2088	1754	3842	5132.350	4244.526	9376.876
Total	**2230**	**1874**	**4104**	**5563.206**	**4560.936**	**10,124.142**
Phase 1						
<4 years	0	0	0	Not applicable (NA)	NA	NA
4 to <16 years	0	0	0	NA	NA	NA
≥16 years	618	288	906	18.727	12.953	31.680
Total	**618**	**288**	**906**	**18.727**	**12.953**	**31.680**
Partial-onset seizure						
<4 years	14	[redacted]	18	39.828	19.017	58.845
4 to <16 years	92	79	171	300.980	200.684	501.665
≥16 years	1300	1287	2587	4743.680	3880.646	8624.326
Total	**1406**	[redacted]	**2776**	**5084.487**	**4100.348**	**9184.835**
Unverricht-Lundborg disease						

Table 1–4: Cumulative study participant exposure to BRV by grouped age and gender

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<4 years	0	0	0	NA	NA	NA
4 to <16 years	0	0	0	NA	NA	NA
≥16 years	50	52	102	238.486	260.761	499.247
Total	**50**	**52**	**102**	**238.486**	**260.761**	**499.247**
Postherpetic neuralgia						
<4 years	0	0	0	NA	NA	NA
4 to <16 years	0	0	0	NA	NA	NA
≥16 years	44	58	102	3.398	4.263	7.661
Total	**44**	**58**	**102**	**3.398**	**4.263**	**7.661**
Essential tremor						
<4 years	0	0	0	NA	NA	NA
4 to <16 years	0	0	0	NA	NA	NA
≥16 years	26	18	44	1.049	0.695	1.744
Total	**26**	**18**	**44**	**1.049**	**0.695**	**1.744**
Other seizure types						
<4 years	12	17	29	26.982	43.693	70.675
4 to <16 years	24	20	44	63.066	53.016	116.082
≥16 years	50	51	101	127.012	85.207	212.219
Total	**86**	**88**	**174**	**217.060**	**181.916**	**398.976**

NA=not applicable

Table 1–3a: Cumulative study participant blinded exposure by grouped age and gender (EP0083 only)

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Cumulative for all indications						
<4 years	0	0	0	Not applicable (NA)	NA	NA
4 to <16 years	0	0	0	NA	NA	NA

Table 1–3a: Cumulative study participant blinded exposure by grouped age and gender (EP0083 only)

Indication Age group	Number of study participants			Subject-years of exposure		
	Male	Female	Total	Male	Female	Total
≥16 years	106	127	233	67.258	72.402	139.661
Total	**106**	**127**	**233**	**67.258**	**72.402**	**139.661**

NA=not applicable

Table 1–5: Cumulative study participant exposure to BRV in ongoing and completed clinical studies by indication and by racial/ethnic origin

Indication Racial/ethnic origin	Number of study participants	Subject-years of exposure
Cumulative for all indications		
American Indian or Alaskan native	52	224.342
Asian	621	1881.561
Black	149	185.194
Native Hawaiian or other Pacific Islander	[redacted]	0.747
White	3057	7112.956
Other	204	690.251
Missing	20	29.092
Total	[redacted]	**10,124.142**
Phase 1		
American Indian or Alaskan native	[redacted]	0.005
Asian	109	3.113
Black	66	2.615
Native Hawaiian or other Pacific Islander	0	NA
White	709	24.964
Other	13	0.312
Missing	[redacted]	0.671
Total	[redacted]	**31.680**
Partial-onset seizure		
American Indian or Alaskan native	51	224.337

Table 1–5: Cumulative study participant exposure to BRV in ongoing and completed clinical studies by indication and by racial/ethnic origin

Indication **Racial/ethnic origin**	**Number of study participants**	**Subject-years of exposure**
Asian	491	1788.359
Black	76	179.061
Native Hawaiian or other Pacific Islander	[redacted]	0.747
White	1968	6325.807
Other	177	638.103
Missing	12	28.422
Total	[redacted]	**1984.835**
Unverricht-Lundborg disease		
American Indian or Alaskan native	0	NA
Asian	0	NA
Black	[redacted]	1.856
Native Hawaiian or other Pacific Islander	0	NA
White	95	477.837
Other	[redacted]	19.554
Total	[redacted]	**499.247**
Postherpetic neuralgia		
American Indian or Alaskan native	0	NA
Asian	0	NA
Black	0	NA
Native Hawaiian or other Pacific Islander	0	NA
White	102	7.661
Other	0	NA
Total	**102**	**7.661**
Essential tremor		
American Indian or Alaskan native	0	NA
Asian	0	NA
Black	0	NA

Table 1–5: Cumulative study participant exposure to BRV in ongoing and completed clinical studies by indication and by racial/ethnic origin

Indication **Racial/ethnic origin**	**Number of study participants**	**Subject-years of exposure**
Native Hawaiian or other Pacific Islander	0	NA
White	44	1.744
Other	0	NA
Total	**44**	**1.744**
Other seizure types		
American Indian or Alaskan native	0	NA
Asian	21	90.089
Black	[redacted]	1.662
Native Hawaiian or other Pacific Islander	0	NA
White	139	274.943
Other	[redacted]	36.282
Total	[redacted]	**398.976**

BRV= brivaracetam; NA=not applicable

Table 1–4a: Cumulative study participant blinded exposure by racial/ethnic origin (EP0083 only)

Indication **Racial/ethnic origin**	**Number of study participants**	**Subject-years of blinded exposure**
Partial-onset seizures		
American Indian or Alaskan native	0	Not applicable (NA)
Asian	233	139.661
Black	0	NA
Native Hawaiian or other Pacific Islander	0	NA
White	0	NA
Other	0	NA
Total	**233**	**139.661**

NA=not applicable

Table 1–6: Cumulative study participant exposure to BRV by dose

Dose	Number of study participants	Subject-years of exposure
5mg/day	58	17.281
20mg/day	151	234.456
25mg/day	[redacted]	0.079
50mg/day	385	1104.654
100mg/day	590	2061.210
150mg/day	887	3465.027
200mg/day	736	2452.454
400mg/day	88	5.240
800mg/day	[redacted]	0.279
100mg	16	0.145
200mg	15	0.041
<50mg	148	2.398
50 to 100mg	261	5.087
100 to <200mg	238	8.934
200 to <400mg	331	13.922
400 to <600mg	63	1.177
≥600mg	59	0.162
0.0 to 1.0mg/kg/day	16	2.152
>1.0 to 2.0mg/kg/day	32	55.962
>2.0 to 3.0mg/kg/day	30	78.272
>3.0 to 4.0mg/kg/day	145	463.937
>4.0mg/kg/day	40	150.653
Missing	[redacted]	0.619
Total	[redacted]	**10,124.142**

BRV= brivaracetam

Table 1–7: Cumulative study participant exposure to BRV by dose in Phase 1 studies

Dose	Number of study participants	Subject-years of exposure
<50mg	148	2.398
50 to <100mg	261	5.087
100 to <200mg	238	8.934
200 to <400mg	331	13.922
400 to <600mg	63	1.177
≥600mg	59	0.162
Total	**906**	**31.680**

BRV= brivaracetam
Note: Study participants may appear in more than 1 BRV dose level

Table 1–8: Cumulative study participant exposure to BRV by dose in study participants with partial-onset seizure

Brivaracetam modal dose	Number of study participants	Study participant-years of exposure
5mg/day	51	14.286
20mg/day	141	189.027
25mg/day	[redacted]	0.079
50mg/day	369	1043.915
100mg/day	537	1808.400
150mg/day	829	3248.879
200mg/day	657	2315.411
0.0 to 1.0mg/kg/day	[redacted]	0.586
>1.0 to 2.0mg/kg/day	21	39.069
>2.0 to 3.0mg/kg/day	23	64.233
>3.0 to 4.0mg/kg/day	102	332.394
>4.0mg/kg/day	34	0.619
Missing	[redacted]	0.619
Total	[redacted]	**9184.835**

BRV= brivaracetam

Table 1–9: Cumulative study participant exposure to BRV by dose in study participants with Unverricht-Lundborg disease

Brivaracetam modal dose	Number of study participants	Study participant-years of exposure
5mg/day	[redacted]	2.992
20mg/day	[redacted]	12.712
50mg/day	11	41.018
100mg/day	37	194.078
150mg/day	37	154.045
200mg/day	[redacted]	94.401
Total	[redacted]	**499.247**

BRV= brivaracetam

Table 1–10: Cumulative study participant exposure to BRV by dose in study participants with postherpetic neuralgia

Brivaracetam modal dose	Number of study participants	Study participant-years of exposure
200mg/day	51	3.885
400mg/day	51	3.775
Total	**102**	**7.661**

BRV= brivaracetam

Table 1–11: Cumulative study participant exposure to BRV by dose in study participants with essential tremor

Brivaracetam modal dose	Number of study participants	Study participant-years of exposure
200mg/day	37	1.465
400mg/day	[redacted]	0.279
Total	[redacted]	**1.744**

BRV= brivaracetam

Table 1–12: Cumulative study participant exposure to BRV by dose in study participants with other seizure types

Brivaracetam modal dose	Number of study participants	Study participant-years of exposure
5mg/day	[redacted]	0.003
20mg/day	[redacted]	32.717
50mg/day	[redacted]	19.721
100mg/day	16	58.732
150mg/day	21	62.103
200mg/day	19	38.757
100mg/day	16	0.145
200mg	15	0.041
0.0 to 1.0mg/kg/day	[redacted]	1.566
>1.0 to 2.0mg/kg/day	11	16.893
>2.0 to 3.0mg/kg/day	[redacted]	14.040
>3.0 to 4.0mg/kg/day	43	131.543
>4.0mg/kg/day	[redacted]	22.716
Total	[redacted]	**398.976**

BRV= brivaracetam

PART II: MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

1.1 Hypersensitivity

- Reason for exclusion:

Hypersensitivity to BRV or any of the excipients is a standard requirement.

- Is it considered to be included as missing information?: No
- Rationale:

As preventive measure, hypersensitivity is a standard exclusion criterion for any investigational medicinal product in a UCB clinical trial. Prescriber information regarding contraindications is provided in the Summary of Product Characteristics (SmPC) Section 4.3. Type I hypersensitivity was added to SmPC Section 4.8.

1.2 Concurrent treatment with levetiracetam

- Reason for exclusion:

This exclusion criterion was specific to some study designs to minimize the risk of biasing data by concurrent administration of a drug with a similar mechanism of action.

- Is it considered to be included as missing information?: No
- Rationale:

There were no safety concerns associated with concurrent treatment of levetiracetam (LEV). Prescriber information regarding concurrent treatment with other antiepileptic drugs (AEDs) including LEV is provided in SmPC Section 4.5.

1.3 Effects of other medicinal products, food, and other substances

- Reason for exclusion:

This exclusion criterion was specific to study designs to reduce variability in systemic exposures to the study drug so that statistical assumptions regarding sample size and effect size were not violated. Therefore, study participants were to be on a stable drug regimen for at least 1 month.

- Is it considered to be included as missing information?: No
- Rationale:

Brivaracetam has a low potential for drug-drug interactions. The extent of absorption of BRV is unchanged by food; therefore, BRV may be taken with or without food.

Interaction studies have only been performed in adults. Brivaracetam plasma concentrations are decreased when coadministered with strong enzyme inducing AEDs (ie, carbamazepine, phenobarbital, phenytoin) but no dose adjustment is required. Prescriber information regarding interaction with other medicinal products and other forms of interaction is provided in SmPC Section 4.5.

1.4 Hepatic impairment

- Reason for exclusion:

This exclusion criterion was specific to study designs to maintain dosing within a typical therapeutic range and to provide a homogeneous study population with study participants in good general health other than the disease being studied.

- Is it considered to be included as missing information?: No.
- Rationale:

Exposure to BRV was increased in adult patients with chronic liver disease. The SmPC reflects this limitation.

1.5 Renal impairment

- Reason for exclusion:

This exclusion criterion was specific to study designs to maintain dosing within a typical therapeutic range and to provide a homogeneous study population with study participants in good general health other than the disease being studied. In general for Phase 2/3 studies, study participants with severe renal impairment were excluded. In view of this exclusion criterion, patients with renal impairment are under-represented in the database. A Phase 1 study was conducted to examine the influence of renal impairment on the pharmacokinetics of BRV in 9 study participants with severe renal impairment (creatinine clearance <30mL/min/1.73m² and not requiring dialysis). Dose adjustment was not found to be necessary.

- Is it considered to be included as missing information?: No.
- Rationale:

Data suggest that BRV does not cause renal toxicity. Brivaracetam has been studied in patients with severe renal impairment. The SmPC reflects this experience and implications for dosing.

1.6 Suicidality

- Reason for exclusion:

A meta-analysis of randomized, placebo-controlled studies of AEDs as a drug class (performed by the Food and Drug Administration; https://www.fda.gov/files/drugs/published/Statistical-Review-and-Evaluation--Antiepileptic-Drugs-and-Suicidality.pdf) has shown a small increased risk of suicidal ideation and behavior. Subsequently, the European Medicines Agency (2008) conducted an independent review and also issued warnings about AEDs and suicidality.

- Is it considered to be included as missing information?: No
- Rationale:

Suicidal ideation and behavior have been reported in patients treated with AEDs, including BRV, in several indications. A meta-analysis of randomized placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for BRV.

Therefore, suicidality was added as an important identified risk.

1.7 Pregnancy

- Reason for exclusion:

Investigational drugs are not routinely given to pregnant women in clinical studies as there are no adequate data to support their use. There are no adequate data on the use of BRV in pregnant women (Section 3). Prescriber information regarding pregnancy is provided in SmPC Section 4.6.

- Is it considered to be included as missing information?: Yes

1.8 Lactation

- Reason for exclusion:

There is insufficient information on the excretion of BRV in human breast milk. There are no adequate data on the use of BRV in pregnant or lactating women (Section 3). Prescriber information regarding pregnancy and lactation is provided in SmPC Section 4.6.

- Is it considered to be included as missing information?: Yes

2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions (occurring ≥1/10,000 to <1/1000), adverse reactions due to prolonged exposure, or those caused by cumulative effects, and those which have a prolonged latency period. Details of these limitations and their implications for the target population are noted in Table 2–1.

Table 2–1: Limitations of adverse drug reaction detection

Ability to detect adverse reactions	Limitation of study program	Discussion of implications for target population
Which are rare (≥1/10,000 to <1/1000)	As of 14 Jul 2020 (for ongoing epilepsy studies), a total of 4572 study participants were included in the brivaracetam (BRV) clinical development program including Phase 1, pediatric, and adult epilepsy exposures. A total of 2437 adult study participants (≥16 years of age, representing 8366.9 subject-years of exposure) were included in Pool S4 [a] (All epilepsy studies pool) that is comprised of study participants from adult Phase 2/3 studies. A total of 262 study participants (representing 743.9 subject-years of exposure) were included in Pool pediatric studies that is comprised of study participants <16 years of age from completed study N01263 and ongoing study N01266.	A substantial amount of data has been collected from the open-label long-term follow-up studies for BRV. However, exposure has not been adequate to ensure that events at the lower end of the "rare" spectrum will have been observed. If a rare event is observed and is considered to be an adverse drug reaction, it will be considered for inclusion in the Summary of Product Characteristics Section 4.8 if it is deemed medically significant. Vigilance will be maintained to identify medically significant rare reactions.
Due to prolonged exposure	In Pool S4 (All epilepsy studies pool), 635 adult study participants (≥16 years of age) have had continuous exposure to BRV for ≥60 months, 443 study participants have had continuous exposure to BRV for ≥90 months, and 113 study participants have had continuous exposure to BRV for ≥120 months. In Pool pediatric studies, 112 study participants have had continuous exposure to BRV for ≥36 months, 87 study participants have had continuous exposure to BRV for ≥48 months, and 71 study participants have had continuous exposure to BRV for ≥60 months.	No risks have been identified that are due to prolonged exposure. Concerns over decreased bone mineral density have been identified for some antiepileptic drugs, in particular enzyme-inducing antiepileptic drugs after prolonged exposure (Ensrud et al, 2008; Stephen et al, 1999). A signal has not been observed with BRV. No effects on bone mineral density were seen in juvenile rats and dogs. The treatment-emergent adverse event of interest specific to the pediatric population (growth, endocrine function/sexual maturation, neurodevelopment, cognitive impairment, anxiety, and depression) was determined to be consistent with what is expected in this population. Vigilance will be maintained to identify events due to prolonged exposure.

Table 2–1: Limitations of adverse drug reaction detection

Ability to detect adverse reactions	Limitation of study program	Discussion of implications for target population
Due to cumulative effects	In Pool S4 (All epilepsy studies pool), 635 adult study participants have had continuous exposure to BRV for ≥60 months, 443 study participants have had continuous exposure to BRV for ≥90 months, and 113 study participants have had continuous exposure to BRV for ≥120 months. In Pool pediatric studies, 112 study participants have had continuous exposure to BRV for ≥36 months, 87 study participants have had continuous exposure to BRV for ≥48 months, and 71 study participants have had continuous exposure to BRV for ≥60 months.	No identified or potential risks due to cumulative effects have been observed for BRV despite long duration of exposure in adults for a clinical program. Vigilance will be maintained to identify any of these effects.
Which have a long latency	As noted above, exposure to BRV has been extensive for a development program but is still insufficient to identify events with a long latency.	Typically, extended follow up in a large number of study participants provides the ability to detect adverse reactions with a long latency. Formal extended follow-up was not considered necessary in the BRV program; however, Investigators were encouraged to report any serious adverse events they considered attributable to BRV without any limitation of time after completion of studies. No signal has been observed. Vigilance will be maintained to identify events which have a long latency.

BRV=brivaracetam

[a] Pool S4 (All epilepsy studies pool) includes completed and ongoing studies in study participants with focal or generalized epilepsy enrolled in adult Phase 2/3 studies who received BRV. These include the following completed studies identified as "core studies": 1 open-label study (N01395) and 6 PBO-controlled studies (5 Phase 2/3 fixed-dose studies [N01114, N01193, N01252, N01253, N01358] and 1 Phase 3 flexible-dose study [N01254]). N01114 included a Conversion Period during which study participants randomized to PBO started treatment with BRV prior to enrollment in follow-up study N01125. All study participants who received BRV during the Conversion Period were included in Pool S4. In addition to these core studies, Pool S4 also includes 4 open-label follow-up studies. These include N01125, N01199, N01372, and N01379 (including study participants from N01258 who received BRV in N01379 and excluding study participants who enrolled in N01372 from N01394).

Data source: ISS Table 1.1A, ISS Table 1.3, 120-day SU Table 4.1.1A, ISS Table 4.1.3

3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 3–1 provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pediatrics (included in preauthorization clinical development program)	The Brivaracetam (BRV) Pediatric Investigation Plan was approved by the (European) Pediatric Committee in Jul 2009, and a development program for BRV in pediatric study participants from ≥1 month to <16 years was initiated. In Pool pediatric studies as of 14 Jul 2020, 262 study participants were exposed to BRV with 743.9 subject-years of exposure. This included 254 study participants (96.3%) with at least 1 month of exposure, 171 study participants (68.0%) with at least 12 months of exposure, 133 study participants (42.5%) with at least 24 months of exposure, 112 study participants (26.5%) with at least 36 months of exposure, 87 study participants (18.7%) with at least 48 months of exposure, and 71 study participants (2.7%) with at least 60 months of exposure.
Elderly (included in preauthorization clinical development program)	As of the 14 Jul 2020 data cutoff date, a total of 117 study participants that were 65 to <75 years of age and 36 study participants that were ≥75 years of age at the time of study entry (including 20 study participants in Phase 1 studies) have received BRV (120-day Safety Update Risk Management Plan Table 1). There were no elderly study participants ≥85 years of age at the time of study entry who were exposed to BRV. Therefore, there is limited data available from clinical trial in the elderly population and none available for the >85-year-old group.
Pregnant and lactating women (not included in preauthorization clinical development program)	Pregnant or lactating women have not been included in BRV clinical studies. As per protocols, if a woman became pregnant during a clinical study, the study drug was stopped, and the subject was discontinued. As of the 14 Jul 2020, 50 pregnancies were reported in BRV treated subjects. From those 46 pregnancies in treated subjects, 1 was ongoing, 20 resulted in early termination; 11 elective/induced abortion and 9 spontaneous abortions. The outcome of 2 pregnancies was unknown as patients were lost to FU. In addition, there were 3 pregnancies reported in partners of BRV-treated subjects, which resulted in 1 healthy full-term baby, 1 low birth-weight premature but healthy baby and 1 elective abortion. Twenty-four pregnancies have resulted in the delivery of 26 live birth babies (including 2 sets of twins) and 2 premature births; there were no reports of congenital malformations. Of note, as these pregnancies were not in direct clinical study participants, they are not included in the clinical database.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
	In conclusion, although there has been no evidence of harm in pregnancies reported during the clinical program, the data are currently insufficient to justify advocating the use of BRV in this population.
Patients with relevant comorbidities: Patients with hepatic impairment (not included in preauthorization clinical development program)	Hepatic impairment: In general for Phase 2/3 studies, study participants with clinically significant hepatic impairment were excluded; in 2 studies, study participants with hepatic enzymes >2 times the upper limit of normal of the reference range were excluded, and in all other studies, study participants with hepatic enzymes >3 times the upper limit of normal of the reference range were excluded. In view of this exclusion criterion, patients with hepatic impairment are under-represented in the database. A Phase 1 study was conducted to examine the influence of hepatic impairment on the pharmacokinetics (PK) of BRV. In N01111, exposure to BRV was increased by 50%, 57%, and 59% in study participants with mild, moderate, or severe chronic liver disease belonging to Child-Pugh classes A, B, and C, respectively, relative to matched healthy controls (Module 5.3.5.3 Integrated Summary of Safety Original Submission Section 9.1.5.2.1). A reduced maximum daily dose is advised for adult and pediatric patients with hepatic impairment (pediatric patients being an extrapolation from adult data). Prescriber information regarding hepatic impairment is provided in Summary of Product Characteristics (SmPC) Section 4.2.
Patients with renal impairment (not included in preauthorization clinical development program)	Renal impairment: In general for Phase 2/3 studies, study participants with moderate-to-severe renal impairment were excluded; in 1 Phase 3 study, study participants with creatinine clearance (CLcr)<30mL/min were excluded, and in all other studies, study participants with CLcr<50mL/min were excluded. In view of this exclusion criterion, patients with renal impairment are under-represented in the database. A Phase 1 study was conducted to examine the influence of renal impairment on the PK of BRV. N01109, a study conducted in 9 study participants with severe renal impairment (CLcr<30mL/min/1.73m² and not requiring dialysis) revealed that the area under the plasma concentration-time curve of BRV was moderately increased (+21% relative to matched healthy controls), while the area under the curves of the acid, hydroxy, and hydroxyacid metabolites were increased 3-, 4-, and 21-fold, respectively. The renal clearance of the metabolites was decreased 10-fold. The safety of the increased exposure to the metabolites was adequately characterized in toxicology studies (electronic Common Technical Document Module 4.2.3.7.5 and Module 4.2.3.2). Since severe renal impairment does not necessitate dose adjustments, the PK of BRV was not studied in study participants with moderate or mild renal

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
	impairment. However, the healthy elderly study participants investigated in N01118 had the characteristics of mild renal impairment (Section 3.2). No data are available in patients with end-stage renal disease undergoing dialysis. Prescriber information regarding renal impairment is provided in SmPC Section 4.2 and SmPC Section 5.2.
Population with relevant different ethnic origin	No BRV clinical studies exclude study participants based on race or ethnic origin. The PK of BRV has been extensively studied in healthy study participants and study participants with epilepsy. No clinically relevant differences were identified between racial groups. Studies were conducted in several countries, including but not limited to countries in North America, Europe, South America, Asia, and Japan and included ethnically diverse populations.
Subpopulations carrying relevant genetic polymorphisms	No data are currently available on synaptic vesicle protein 2A (SV2A) polymorphisms in relation to BRV efficacy or safety; however, a homozygous mutation in the SV2A gene in a patient with intractable epilepsy was reported (Serajee and Huq, 2015). The report provides evidence that an SV2A mutation can be a cause of epilepsy in humans. The patient with the SV2A mutation did not respond to levetiracetam. The location of the mutation in this patient supports an important role of adenine nucleotide binding in SV2A function. [redacted] Regarding BRV disposition, formation of the hydroxy metabolite is supported by cytochrome (CYP) 2C19. There was only a modest increase in exposure (n=9 poor metabolizers) in study participants carrying 2 alleles of the non-functional mutation *2 or *3 of CYP2C19, while production of the hydroxy metabolite exhibited a 10-fold decrease. Prescriber information regarding pharmacokinetic properties (biotransformation) is provided in SmPC Section 5.2.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Other relevant comorbidities: • Cognitive impairment • Psychiatric symptoms (depression, anxiety, and suicidality)	In clinical studies with BRV, inclusion/exclusion criteria excluded study participants who had severe uncontrolled psychiatric conditions. Upon the introduction of the Columbia-Suicide Severity Rating Scale through protocol amendments (designed to help the investigator determine suicidal ideation/behavior), those study participants with a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) or those who had suicidal ideation in the past 6 months were excluded from studies. Study participants already enrolled in clinical studies who presented a lifetime history (prior to study entry or since study start) of suicide attempt or who had active suicidal ideation at the time of the assessment or recalled active suicidal ideation/behaviors were withdrawn. In the majority of studies within the program, BRV has been used as adjunctive therapy; therefore, attributing causality of the symptoms of these comorbid conditions to BRV is difficult. However, BRV does not appear to have had a significant negative impact on these comorbid conditions. Product labeling reflects what has been observed in the program.

BRV=brivaracetam; CLcr =creatinine clearance; CYP=cytochrome; PK=pharmacokinetic; SmPC=summary of product characteristics; SV2A=synaptic vesicle protein 2A

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PART II: MODULE SV: POSTAUTHORIZATION EXPERIENCE

1 METHOD USED TO CALCULATE EXPOSURE

A conservative view was adopted by assuming that all patients receive complete dosage regimens at the time of treatment. Patient exposure is estimated using the available UCB sales data from 01 Jan 2016 to 30 Jun 2020 for the cumulative time interval. Note that sales data are only available to UCB on a month to month basis.

The defined daily dose (DDD) is assumed to be 100mg according to the World Health Organization (WHO). For calculation purposes, a year is defined as 365.25 days and a month is defined as 30 days.

$$\text{Patient years} = \frac{\text{(total milligrams of product distributed)/DDD}}{\text{365.25 days in year}}$$

where 0.25 is added to account for leap years.

2 EXPOSURE

Cumulatively, 9,046,352,580mg of BRV has been distributed worldwide from 01 Jan 2016 to 30 Jun 2020, contributing to approximately 247,676 patient-years.

Data on cumulative exposure by region and formulation are presented in Table 2–1 and Table 2–2 , respectively.

Table 2–1: Cumulative patient exposure by region till 30 Jun 2020

Region	Country	Patient-years for the cumulative interval
European Economic Area (EEA)	Austria	[redacted]
	Belgium and Luxembourg	[redacted]
	Bulgaria	[redacted]
	Czech Republic	[redacted]
	Denmark	[redacted]
	Finland	[redacted]
	France	[redacted]
	Germany	[redacted]
	Greece	[redacted]
	Hungary	[redacted]
	Ireland	[redacted]
	Italy	[redacted]
	Netherlands	[redacted]
	Norway	[redacted]

Table 2–1: Cumulative patient exposure by region till 30 Jun 2020

Region	Country	Patient-years for the cumulative interval
	Poland	[redacted]
	Romania	[redacted]
	Slovakia	[redacted]
	Slovenia	[redacted]
	Spain	[redacted]
	Sweden	[redacted]
	United Kingdom	[redacted]
Asia Pacific (Australia)		[redacted]
Europe(non-EEA) Switzerland		4509 [redacted]
Latin America		4084
Middle East & Africa		3654
US and Canada		[redacted]
Other		3181[a]
Total		**247,676**

EEA= European Economic Area
[3181] Includes sample distribution to the US (US and Puerto Rico)

Table 2–2: Cumulative patient exposure by formulation till 30 Jun 2020

Dosage form	Patient-years for the cumulative interval
Film-coated tablet	238,770
Oral solution	8509
Solution for infusion	396
Total	**247,676**

Postmarketing data are not available by age group or by gender.

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

As a member of the racetam class of compounds, BRV possesses a high structural similarity to LEV, an AED that has no restrictions on its prescriptions as it is not associated with abuse. It is not structurally related to any AEDs known to be abused or examples of all of major classes of recreationally abused sedative euphoriant drugs, including barbiturates, benzodiazepines, cannabinoids, opiate and opioid-like compounds, or dissociative anesthetics. As BRV is not a known precursor of a controlled substance or structurally related to existing drugs of abuse, it is unlikely that it could be used in the manufacture of a controlled substance. In the US, BRV is classified under Schedule V.

At concentrations up to 10µM, BRV did not induce a significant displacement (>50%) of radioligands specific for 50 other binding sites within the CNS, including various receptors, uptake systems, and ion channel proteins (electronic Common Technical Document Module 4, Report RRLE01E1509). After systemic administration in mice, BRV produced dose-dependent occupancy of the central synaptic vesicle protein 2A (SV2A) binding site. Occupancy of 50% central SV2A binding sites was obtained at a dose of 3.3µmol/kg (0.7mg/kg) (CNS11024). Brivaracetam binds with high selectivity and affinity to SV2A; however, SV2A binding is not known to be associated with drug abuse. In summary, the binding profile of BRV shows high selectivity for SV2A and no apparent binding to other CNS targets.

It is well known that drug abusers use routes of administration other than the intended clinical route. Such routes include intravenous injection, intranasal insufflation (“snorting”), and smoking. The intravenous formulation of BRV will only be available in a hospital setting, and hence, access will be limited. Brivaracetam is very soluble in aqueous solvents, such as water, that might be considered as a vehicle for intravenous injection. Given that BRV is also highly permeable, it may be absorbed by the mucous membranes when taken intranasally; however, the quantity of the drug required to achieve supratherapeutic doses needed to induce subjective effects would be a limiting factor for this route. Specifically, because BRV will be commercially available only in dosage strengths up to 100mg, 10 tablets would be required to achieve a 1000mg dose. Given a weight of 540mg per tablet, this would represent 5.4g of material. Previous studies have suggested that some experienced intranasal abusers may encounter difficulties insufflating more than about 400mg to 500mg of powder, and 1 to 2g is the maximum that most abusers could insufflate at 1 time. Therefore, the bulk of the tablets would likely deter abusers from insufflating large doses of BRV. While there are no data on higher temperatures with BRV to evaluate smoking potential, all of these alternative routes of administration are unlikely given the types of subjective effects observed with BRV and the minimal abuse associated with related drugs (such as LEV). The oral solution and intravenous solution are not considered relevant for intranasal abuse as they are not solid dosage forms that can be powderized for insufflation, and the concentration of the solutions is considered a limitation to intranasal administration of the liquid (ie, 10mg/mL).

In the clinical development program, there were no reports of abuse, misuse, dependence, or withdrawal with BRV. Across all study pools, dizziness, somnolence, fatigue, and asthenia were the most common CNS events of interest. The incidence of euphoric mood and feeling drunk

was low in patient populations, but higher in Phase 1 populations. Reports of hallucinations, stimulant-related, dissociative/psychotic, mood disorders, and motor/cognitive impairment events were infrequent in most populations. Overall, the pattern and incidence of treatment-emergent adverse event (TEAEs) of interest were consistent with those observed with other AEDs.

No medication diversions were reported. No additional evidence of diversion or excessive drug taking was found in protocol deviation listings, early discontinuation records, and compliance information for BRV pivotal studies. Brivaracetam is a prescription drug and will be distributed by regionally established and controlled distribution lines. Therefore, the potential for diversion is minimized.

Drug abuse potential study (N01295)

A study was conducted to assess the drug abuse potential of BRV. N01295 was a Phase 1, randomized, double-blind, triple-dummy, PBO, unscheduled and scheduled comparator-controlled study. Study participants received single doses of BRV 50mg, BRV 200mg, BRV 1000mg, LEV 4000mg (negative control), alprazolam 1.5mg (positive control), alprazolam 3mg (positive control), and PBO administered orally according to a 7-way crossover design.

The primary and secondary variables included measures of the following:

- Balance of effects: drug liking, overall drug liking, and take drug again visual analog scales (VASs)
- Positive/euphoria effects: high and good drug effects VAS and Addiction Research Center Inventory (ARCI) morphine-benzedrine group
- Sedative effects: ARCI pentobarbital chlorpromazine alcohol group and ARCI benzedrine group (BG) minimum effect
- Other subjective effects: any drug effects and dizziness VAS

Brivaracetam showed fewer sedative, euphoric, stimulant (ARCI amphetamine and ARCI BG maximum effect), dizziness, and negative effects on the subjective measures compared to alprazolam; however, BRV was not significantly different from alprazolam on some measures of balance and positive effects at the supratherapeutic doses. Both BRV and LEV showed balance, positive, negative, sedative, and other subjective effects greater than PBO, and overall, the subjective effects of BRV were very similar to those of LEV. On balance effects and positive/euphoria effects variables, BRV 50mg and 200mg were not significantly different from LEV, while the BRV 1000mg dose showed small, but statistically greater, effects. The BRV 200mg dose also showed slight, but significantly greater, effects on good drug effects. However, both BRV 200mg and BRV 1000mg were significantly greater than LEV 4000mg on the any drug effects VAS, indicating that the differences may have been due to greater perception of effects overall due to the higher relative dosing. Negative effects, dizziness, sedative effects, and mild stimulant-like effects were not different between LEV and any dose of BRV.

The results of N01295 demonstrate that although abuse potential cannot fully be ruled out at this time, there were differences in the subjective effects profile between BRV and alprazolam, and the effects were much more similar to those of LEV, an AED that is not known to be abused.

In summary, there is minimal potential for the abuse of BRV. Routine pharmacovigilance since license approval has not identified any additional safety concerns and sufficient data on this risk have been obtained and reviewed. Furthermore, any occurrence is considered so infrequent that additional pharmacovigilance activities are unlikely to afford further relevant information. Hence, abuse potential (as a CNS-active product) is reclassified as a not important potential risk for BRV.

PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

This section is not applicable as this is not an initial RMP.

2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns were identified. No safety concerns were reclassified.

3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Data from the primary placebo (PBO)-controlled epilepsy studies pool (Pool S1), all epilepsy studies pool (Pool S4), and all pediatric study participants in studies N01263 and N01266 pool (Pool pediatric studies) are discussed within this EU-RMP. The data pools are defined in Table 3–1.

Table 3–1: Overview of safety pools

Pool/Data cutoff date	Pool definition	Studies included
Study participants enrolled in adult Phase 2/3 studies[a]		
Pool S1/ 17 Jan 2014	Study participants receiving at least 1 dose of placebo (PBO) or brivaracetam (BRV) from the Phase 3 PBO-controlled, fixed dose epilepsy studies	N01252, N01253, and N01358
Pool S4/ 15 Mar 2017	Study participants receiving at least 1 dose of BRV in all epilepsy short- and long-term studies	N01114, N01193, N01252, N01253, N01254[b], N01358, N01395, and N01125 (excluding study participants with Unverricht–Lundborg disease), N01199, N01372, N01379 (includes study participants from N01258 only if they received BRV in N01379)
Other study participants		
Pool pediatric studies/ 15 Mar 2017	Study participants <16 years of age receiving at least 1 dose of BRV in any pediatric Phase 2/3 clinical study	N01263 and N01266

BRV=brivaracetam; PBO=placebo

[a] The age of study participants in adult Phase 2/3 studies as defined by the respective study inclusion criteria was 16 years of age and older.

[b] N01254 was a flexible dose study.

Data source: ISS Original Submission Table 1.1.1 and Table 1.1.4

3.1 Presentation of important identified risks and important potential risks

3.1.1 Important identified risk: Suicidality

3.1.1.1 Potential mechanisms

No clear mechanism for suicidality associated with AEDs has been identified. It has been suggested that AEDs increase the incidence of psychiatric adverse events associated with an increased suicidal risk, especially in AEDs that have gamma-aminobutyric acid (GABA)-ergic properties (Kalinin, 2007). Brivaracetam has no effect on GABA- and glycine-gated currents. However, other AEDs without known GABAergic effects have been associated with an augmented incidence of psychiatric adverse events that can lead to increased suicidality, but the potential pathogenic mechanisms remain to be established (Clarke et al, 2012; Karouni et al, 2010; Mula and Sander, 2007).

The relationship between epilepsy and suicidality is complex and multifactorial. Factors involved in the etiology of suicidality in epilepsy include epilepsy-related variables, personal and familial psychiatric history, and iatrogenic effects. Furthermore, a bidirectional relationship between psychiatric disorders such as depression and epilepsy has suggested the existence of common neurobiological pathogenic mechanisms including disturbances of secretion of several neurotransmitters, particularly serotonin, norepinephrine, glutamate, and GABA, and disturbances of the hypothalamic–pituitary–adrenal axis, which in turn, can increase the risk of suicidality (Hecimovic et al, 2011). Additionally, there is a large subset of patients experiencing increased psychiatric symptoms while on AED that are not explained by the known drug-related mechanisms, suggesting more work needs to be done to understand the biological processes leading to these effects (Mula and Sander, 2013).

3.1.1.2 Evidence source(s) and strength of evidence

A meta-analysis of randomized, PBO-controlled studies of AEDs as a drug class (performed by the FDA in 2008) has shown a small increased risk of suicidal ideation and behavior.

Suicidal ideation, attempt, and completed suicide have been observed within the BRV program, but not at the statistical threshold currently nominated for inclusion as expected adverse drug reactions (incidence rate ≥1% in the BRV total group and which are >1% more than PBO, based on the BRV total group).

3.1.1.3 Characterization of the risk

Frequency with 95% CI:

Clinical development

Pool S1

In Feb 2011, the FDA notified UCB of their policy based on the “Draft Guidance for Suicidality: Prospective Assessment of Occurrence in upon Clinical Trials” that an assessment of suicidal ideation and suicidal behavior based on the Columbia Suicide Severity Rating Scale (C-SSRS) was to be added to all ongoing studies of central nervous system drugs. It is recognized that the introduction of C-SSRS into studies (including N01358) that were already ongoing had the potential to result in a higher number of reported suicidal events following implementation and a subsequent exclusion of study participants with more serious psychiatric conditions, eg, before

introduction of C-SSRS, the entry criteria for studies allowed enrollment of study participants with a history of a suicide attempt; after inclusion of C-SSRS in studies, these study participants were excluded from enrollment.

In Pool S1 (primary PBO-controlled epilepsy studies pool), 46 study participants (4.2%) in the BRV-treated group and 10 study participants (2.2%) in the PBO group reported at least 1 treatment-emergent adverse event (TEAE) of interest potentially associated with suicidality; there was no apparent relationship between BRV dose and incidence across the proposed therapeutic range (BRV 50mg/day to BRV 200mg/day) (ISS Original Submission Table 5.11.8.1.1).

Pool S4

In Pool S4 (all epilepsy studies pool), TEAEs of interest potentially associated with suicidality were reported in 81 BRV-treated study participants (3.3%) (ISS Table 5.14.3.1.3). When corrected for subject-years of exposure, the incidence rate of TEAEs of interest potentially associated with suicidality was 0.98 per 100 subject-years (95% CI: 0.78, 1.22) (ISS Table 5.14.18.3).

In Pool S4, the most commonly reported TEAE of interest potentially associated with suicidality in the BRV-treated group was suicidal ideation (60 study participants [2.5%]). For the BRV-treatment group, 18 study participants (0.7%) reported TEAEs of suicide attempt, [redacted] reported TEAEs of self-injurious ideation, [redacted] each reported TEAEs of completed suicide and intentional self-injury, and [redacted] each reported TEAEs of intentional overdose, depression suicidal, and self-injurious behavior (ISS Table 5.14.3.1.3).

There was no apparent relationship between the duration of BRV treatment and TEAEs potentially associated with suicidality in Pool S4. The incidence of TEAEs potentially associated with suicidality was low (≤0.7%) during any given 3-month safety time interval. During Months 130 through 168, no study participants reported TEAEs potentially associated with suicidality (ISS Table 5.14.3.2.3).

In Pool S4 (all epilepsy studies pool), the most commonly reported TEAEs that led to permanent discontinuation of the study drug in the BRV-treated group were suicidal ideation (18 study participants [0.7%]), suicide attempt (14 study participants [0.6%]), completed suicide ([redacted]), and self-injurious behavior ([redacted]) (ISS Table 5.6.3).

In the BRV-treated group in Pool S4, serious TEAEs of interest potentially associated with suicidality included suicidal attempt (18 study participants [0.7%]), suicidal ideation (14 study participants [0.6%]), completed suicide ([redacted]), and self-injurious ideation ([redacted]) (ISS Table 5.5.3).

- Treatment-emergent serious adverse events (SAEs) of completed suicide were reported for [redacted]: [redacted] in the BRV 100mg/day group had a history of depression and [redacted] in the BRV 150mg/day group had poor seizure control in the preceding days. [redacted] study participants had been exposed to BRV for more than 6 months with no recent dose changes (ISS Original Submission Table 5.11.18.6).

- In addition, there were [redacted] fatal cases reported, for which suicidality could not be excluded as a cause because of lack of witnesses and available details.
- In Pool S4, a total of 24 cases were reported for either completed suicide or suicide attempt. These included [redacted] cases of completed suicide and [redacted] fatal cases, for which suicidality could not be excluded, 18 cases of reported suicide attempt, and [redacted] cases of possible suicide attempt.
- Five of the 24 cases occurred within the first 6 months of treatment with BRV.

Pool pediatric studies (all pediatric study participants in studies N01263 and N01266)

- In Pool pediatric studies, [redacted] reported at least 1 TEAE potentially associated with suicidality. When corrected for subject-years of exposure, the incidence rate of TEAEs potentially associated with suicidality was 1.97 per 100 subject-years (95% CI: 0.90, 3.74) (120-day SU Table 5.14.18.1A). The most commonly reported TEAE potentially associated with suicidality in the BRV overall group was suicidal ideation ([redacted]). [redacted] reported the TEAE of self-injurious behavior. [redacted] each reported a TEAE of intentional self-injury and suicide attempt (120-day SU Table 5.14.3.1.1A). No study participant completed suicide.
- In Pool pediatric studies, the incidence of TEAEs potentially associated with suicidality was highest during Months 1 to 3 ([redacted]) and decreased thereafter: during Months 4 to 60 (0[redacted]) and after Month 61 (0 study participants) (120-day SU Table 5.14.3.2.1A).
- In Pool pediatric studies, the TEAE of suicidal ideation led to permanent discontinuation of the study drug in [redacted] (120-day SU Table 5.6.1A).
- In the BRV-treated group in Pool pediatric studies, serious TEAEs potentially associated with suicidality included suicidal ideation ([redacted]) and suicide attempt ([redacted]) (120-day SU Table 5.5.1A). The suicide attempt occurred within the first 6 months of treatment [redacted].

Pool pediatric studies (study participants ≥4 to <16 years with partial-onset seizures)

Of study participants aged ≥4 to <16 years with partial-onset seizures (POS), [redacted] reported suicidal ideation, including [redacted] who attempted suicide 10 days after discontinuing BRV treatment. In [redacted], the TEAE of suicidal ideation occurred within the first 3 months of BRV initiation. All events were mild and nonserious, except 1 event that was a severe SAE. [redacted] events resolved and were considered not related to BRV by the investigator. Five TEAEs of suicidal ideation started the same day (±1 day) the C-SSRS assessment was performed, which could suggest that the assessment triggered the reporting of these events. No study participant completed suicide. When corrected for subject-years of exposure, the incidence rate of TEAEs of interest potentially associated with suicidality in pool pediatric study participants with POS was 1.41 per 100 subject-years (95% CI: 0.68, 2.59) (120-day SU Table 5.14.18.1B).

Postmarketing

Based on the review of the postmarketing data in the frame of the PSUR analysis, no change in the characterization of this important identified risk is proposed. There is no evidence of an increased risk of suicidality in the pediatric population.

Severity:

Clinical development

In Pool S1 (primary PBO-controlled epilepsy studies pool), [redacted] BRV-treated study participants ([redacted]) and no PBO-treated study participants reported at least 1 TEAE potentially associated with suicidality that had an intensity of severe (ISS Original Submission Table 5.11.18.1).

In Pool S4 (all epilepsy studies pool), TEAEs potentially associated with suicidality that had a maximum intensity of severe included suicide attempt (15 study participants [0.6%]), suicidal ideation ([redacted]), completed suicide ([redacted]), and self-injurious ideation ([redacted]) (120-day SU Table 5.4.1.3).

In Pool pediatric studies (all pediatric study participants in studies N01263 and N01266), [redacted] had a TEAE potentially associated with suicidality (suicidal ideation) that had an intensity of severe (120-day SU Table 5.4.1.1A).

Background incidence/prevalence:

The incidence of suicide-related events in individuals who have epilepsy is significantly higher than that in the general population. The proportion of patients with epilepsy who have current suicidal ideation is approximately 12.2%; the lifetime prevalence of suicidal ideation ranges from 25.5% to 26.5%. The lifetime prevalence of suicide attempts ranges from 12.5% to 20.8%, and deliberate self-harm is approximately 12.7% (Rai et al, 2012; Tellez-Zenteno et al, 2007; Jones et al, 2003). Not only do people living with epilepsy have a higher risk of suicide but they also people with a history of suicidal ideation and behavior have a 5-fold higher risk of developing epilepsy than controls (Hesdorffer et al, 2006). The incidence of suicide-related events (ie, attempted suicide, intentional self-inflicted injuries, and suicide) from community-based studies has been estimated to be 15.0 (95% CI: 14.6 to 15.5) per 100,000 person-years among patients without epilepsy and not taking AEDs, 38.2 (95% CI: 26.3 to 53.7) per 100,000 person-years among patients with epilepsy not taking AEDs, and 48.2 (95% CI: 39.4 to 58.5) per 100,000 person-years among patients with epilepsy receiving AEDs (Arana et al, 2010).

Another community-based study using US commercial insurance claims data from HealthCore Integrated Research Database assessed suicidality in patients aged at least 15 years who had incident use of AEDs (absence of anticonvulsant medication in the 6 months before the index date). The study excluded individuals who had a recorded history of attempted suicide or medical conditions that could have influenced the risk of suicidal acts. Suicidality-related events assessed included suicide attempts, completed suicide, or violent death in patients who were prescribed anticonvulsants (carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, LEV, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproate, and zonisamide) between Jul 2001 and Dec 2006. The incidence rate of suicide ranged from 6.2 per 1000 person-years in patients exposed to primidone to 34.3 per 1000 person-years in patients exposed to oxcarbazepine (Patorno et al, 2010). A meta-analysis was conducted by the FDA using data from 199 randomized parallel-arm PBO-controlled studies with 27,863 AED study participants and 16,029 PBO controls, with a mean study duration of 12 weeks to assess the risk of suicidal thoughts and acts in patients exposed to AEDs. The meta-analysis reported an increased risk of suicidality associated with all AEDs including carbamazepine, divalproex sodium, felbamate, lamotrigine, gabapentin, LEV, oxcarbazepine, pregabalin, tiagabine,

topiramate, and zonisamide. Among the epilepsy indication, suicidality occurred in 3.53 per 1000 study participants treated with AEDs compared with 1.0 per 1000 study participants in the comparator arms (RR: 3.5; 95% CI: 1.28 to 12.1; FDA, 2008). Subsequently, the EMA conducted an independent review and also issued warnings about AEDs and suicidality (http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/PhVWP_Recommendations/AntiEpileptics/AntiEpileptics_Key_statement_2008_07.pdf).

These findings resulted in the class labeling of AEDs. However, a meta-analysis conducted by the World Psychiatric Association Section on Pharmacopsychiatry on published literature up to Dec 2014 concluded that available data (including the FDA meta-analysis) do not support the presence of a "class effect" of antiepileptics in inducing any type of suicide-related behaviors (Fountoulakis et al, 2015). Some of the methodological limitations that might have had an impact on the results of the FDA meta-analysis include biased selection of studies (33 out of 199 studies were included in the main analysis) and retrospective nonsystematic collection of suicidality data (Rudzinski and Meador, 2011). Further, there is evidence of an increase risk of suicide attempt among patients with epilepsy even before they are symptomatic, suggesting etiologic pathways exist above and beyond those attributable to AED-related risks (Hesdorffer et al, 2016). Also, suicidal ideation is not unexpected in the adolescent population. A Youth Risk Behavior Survey conducted by the CDC in 2015 showed that 17.7% students seriously considered suicide in the 12 months prior to the survey (Kann et al, 2016).

Long-term outcomes:

The effects of suicidal ideation on the person who has suicidal thoughts and takes action on those thoughts may include severe injury, brain damage, brain death, damage to all organ systems, seizures, coma, and death.

Impact on quality of life:

Suicidality can vary greatly in severity from thoughts or ideas through fatal completion of suicide.

3.1.1.4 Risk groups factors or risk factors

The risk of suicide-related events is higher in individuals with severe epilepsy, temporal lobe epilepsy, and following epilepsy-related surgery (Arana et al, 2010). Additionally, individuals with comorbid psychiatric disorders have a higher risk of suicide within the epilepsy population (Tellez-Zenteno et al, 2007). Epilepsy patients with a previous suicide attempt are at a 40% greater risk of a completed suicide (Harris and Barraclough, 1997). The risk is also increased in the first 6 months after epilepsy diagnosis (Christensen et al, 2007). There is a notable increase in suicidal ideation postictally in patients with refractory partial epilepsy, with 13% patients reporting suicidal ideation within 72 hours in over half of their seizures. There are also sex differences in risk factors for suicide among patients with epilepsy. Earlier age of onset is associated with increased risk for men, but not women (Verrotti et al, 2008).

3.1.1.5 Preventability

Risk factors associated with suicide in epilepsy should be monitored. This includes a personal or family history and current psychiatric illness, particularly affective symptoms. Early identification and management of psychiatric conditions in patients with epilepsy can reduce the risk of suicide-related events (Hesdorffer and Kanner, 2009). The risk factors can be managed by

educating patients and care providers about neuropsychiatric symptoms in epilepsy, avoiding or carefully monitoring AEDs with relatively higher risk of neuropsychiatric complications in patients who may be predisposed to psychiatric comorbidity and, where appropriate, timely psychiatric referral (Bagary, 2011). There is growing evidence that children with epilepsy are similarly at an elevated risk of suicide. Relative to children without epilepsy, they experience more psychological disorders and injury associated with suicide risk (Jones et al, 2003). As a result, increased monitoring of psychiatric symptoms in children with epilepsy has also been recommended (Zamani et al, 2012). Patients should be monitored for signs of suicidal ideation and behaviors and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should any signs of suicidal ideation or behavior emerge (SmPC Jones et al, 2003; and SmPC Section 4.8).

3.1.1.6 Impact on the risk-benefit balance of the product

Routine pharmacovigilance activities are considered sufficient to monitor this risk. The C-SSRS is used in all clinical studies to assess the suicidal ideation and suicidal behavior in study participants (in study participants aged <6 years, the symptoms and signs of depression are recorded).

The well-characterized risk of suicidality has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining favorable.

3.1.1.7 Public health impact

Population-based studies have reported proportionate mortality ratios of 0 to 7% for suicide in patients with epilepsy (Lhatoo et al, 2001; Lindsten et al, 2000). Suicides contributed 6.7% of estimated excess years of potential life lost among patients with epilepsy in the US and 4.2% in the UK in 2010 (Nevalainen et al, 2015). Suicide also made up 4.3% deaths among children (aged 0 to 18 years) with epilepsy in a South Carolina population surveillance between 2000 and 2011 (Selassie et al, 2014).

3.2 Presentation of the missing information

3.2.1 Data during pregnancy and lactation

3.2.1.1 Evidence source

There are no adequate data from the use of BRV in pregnant or lactating women. Brivaracetam is not recommended for use in pregnant women. In nonclinical studies, BRV did not affect male or female fertility and has demonstrated no teratogenic potential in either rats or rabbits. Brivaracetam induces a dose-related increase in the concentration of the active metabolite carbamazepine-epoxide (CBZ-E), which is potentially teratogenic when carbamazepine is taken concomitantly to BRV. There are insufficient data to determine the clinical significance of this effect in pregnancy.

3.2.1.2 Population in need of further characterization

The safety and efficacy in pregnant or breastfeeding women have not been established.

It is unknown whether BRV is excreted in human breast milk. Studies in rats have shown excretion of BRV in breast milk. A decision should be made whether to discontinue breastfeeding or to discontinue BRV, taking into account the benefit of the medicinal product to the mother. In case of coadministration of BRV and carbamazepine, the amount of CBZ-E

excreted in breast milk could increase. There are insufficient data to determine the clinical significance.

Anticipated risk/consequence of the missing information: The potential risk for humans is unknown.

3.2.2 Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients

3.2.2.1 Evidence source

The available clinical experience with BRV to date has not shown any effect on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients.

One study showed lower mean brain weight in high dose-treated juvenile rats at a dose inducing marked toxicity, ie, mortality, clinical signs, and decreased body weight. There were no findings recorded during neuropathological and histological examinations and no deleterious effects on behavioral functionality. No clinical concerns have been reported to date from 1 completed PK study in 99 study participants (N01263) and 1 ongoing long-term follow-up study (N01266). By 14 Jan 2020, 259 study participants aged >1 month and ≤16 years had received BRV.

3.2.2.2 Population in need of further characterization

Pediatric patients will be further characterized for the following safety concerns: growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development.

Anticipated risk/consequence of the missing information: The anticipated risk/consequence of this missing information is unknown.

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PART II: MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

A summary of safety concerns for BRV is provided in Table 1–1.

Table 1–1: Summary of safety concerns

Important identified risks	Suicidality (class label for anticonvulsant products)
Important potential risks	None
Missing information	Data during pregnancy and lactation Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, cognitive and psychomotor development in pediatric patients

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION STUDIES)

1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

- Other forms of routine pharmacovigilance activities:

The Columbia Suicide Severity Rating Scale is used in all clinical studies to assess suicidal ideation and suicidal behavior in subjects (symptoms and signs of depression are recorded in subjects aged <6 years).

2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities include the following:

- Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) and in the North American AED Pregnancy Registry

Prescribers and reporters of pregnancy cases are encouraged to register pregnant women exposed to AEDs into the EURAP and North American AED Pregnancy Registry. References to registries are included in the pregnancy follow-up letter, US Call Center script, and information for Medical Science Liaisons.

3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table 3–1.

Table 3–1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				

Table 3–1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy Ongoing	To collect data on pregnancy	Pregnancy and lactation	Start of data collection Completion of data collection Interim study report	Cumulative data appearing in these registries are discussed in Periodic Safety Update Reports (PSURs)
Participation in and sponsorship of North American Antiepileptic Drug Pregnancy Registry Ongoing	To collect data on pregnancy	Pregnancy and lactation	Start of data collection Completion of data collection Interim study report	Cumulative data appearing in these registries are discussed in PSURs

PSUR=periodic safety update report

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations for BRV.

RMP PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

1 ROUTINE RISK MINIMIZATION MEASURES

Description of routine risk minimization measures by safety concern is presented in Table 1–1 .

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks:	
Suicidality	Routine risk communication: Section 4.4, Special Warnings and Precautions for Use, of the Summary of Product Characteristics (SmPC; class wording) and Section 4.8, Undesirable Effects, of the SmPC Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measure beyond the Product Information: Available by prescription only Packaging: • The brivaracetam (BRV) oral tablet pack contains unit dose packaging (blister) that requires a sequential withdrawal of the tablets, which could interfere with accomplishment of suicidal thoughts. • Intravenous formulation is provided in vials containing 50mg of BRV in total, and the administration will be performed by a healthcare professional and not the patient. • Oral solution is packaged in bottles with 300mL fill volumes with a concentration of BRV 10mg/mL. This corresponds to 3g of BRV if the entire volume is taken. Once placed, the adaptor for the 5 or 10mL oral-dosing syringe is difficult to remove, thus limiting the ability to drink significant volume. The oral solution, although flavored, does not have a pleasant taste due to the bitter tasting drug substance.
Important potential risks: None	
Missing information:	
Pregnancy and lactation	Routine risk communication: Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measure beyond the Product Information: Available by prescription only

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measure beyond the Product Information: Available by prescription only

BRV=brivaracetam; SmPC=summary of product characteristic

2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V Section 1 are sufficient to manage the safety concerns of the medicinal product. Additional risk minimization measures are not considered necessary.

3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 3–1 provides a summary table of pharmacovigilance activities and risk minimization by safety concern.

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Suicidality (class label for anticonvulsant products)	Routine risk minimization measures: Available by prescription only Section 4.4, Special Warnings and Precautions for Use, of the Summary of Product Characteristics (SmPC; class wording) and Section 4.8, Undesirable Effects, of the SmPC Packaging Additional risk minimization measures: None	Routine pharmacovigilance (PV) activities beyond adverse reactions reporting and signal detection: The Columbia-Suicide Severity Rating Scale used in all clinical studies (in subjects aged <6 years, the symptoms and signs of depression are recorded) Additional PV activity: None

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Data during pregnancy and lactation	Routine risk minimization measures: Available by prescription only Section 4.6, Fertility, Pregnancy and Lactation of the SmPC Additional risk minimization measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activities: Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy and North American Antiepileptic Drug Pregnancy Registry. Activities include provision of requested data from UCB to the registries and regular review of interim outputs from the registries.
Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients	Routine risk minimization measures: Available by prescription only Additional risk minimization measures: None	Routine PV activities beyond adverse reactions reporting and signal detection: None Additional PV activity: None

PV=pharmacovigilance; SmPC=summary of product characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for brivaracetam

This is a summary of the Risk Management Plan (RMP) for Briviact® (brivaracetam). The RMP details the important risks of Briviact, how these risks can be minimized, and how more information will be obtained about the risks and uncertainties (missing information) associated with Briviact

The Summary of Product Characteristics (SmPC) and Package Leaflet for Briviact give essential information to healthcare professionals and patients on how Briviact should be used.

This summary of the RMP for Briviact should be read in the context of all this information including the assessment report of the evaluation and its plain language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates to the Briviact RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Brivaracetam is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy (see SmPC for the full indication). It contains brivaracetam as the active substance, and it is given as oral tablet of the strengths 10mg, 25mg, 50mg, 75mg, and 100mg film-coated tablets; as 10mg/mL oral solution; or as 10mg/mL solution for injection/infusion.

Further information about the evaluation of Briviact's benefits can be found in its EPAR, including in its plain language summary, available on the European Medicines Agency website, under the medicine's webpage (http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/003898/human_med_001945.jsp).

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Briviact, together with measures to minimize such risks and the proposed studies for learning more about Briviact's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be as follows:

Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals. Additional details in the tables displaying the volume (according to the patient's body weight and dose) to be taken with the individual syringe included in the Package Insert Leaflet; color-coded syringes matching the pictograms displayed on the carton box; inclusion of clear and detailed instructions in the PIL. In the case of Briviact, routine risk minimization measures are considered sufficient to address the safety concerns of this medicinal product. Therefore, additional risk minimization measures are not considered necessary.

- Important advice on the medicine's packaging.

- The authorized pack size — the amount of medicine in a pack is chosen in a way to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Briviact is not yet available, it is listed under "missing information" in Table 2–1.

2.1 List of important risks and missing information

Important risks of Briviact are those that need special risk management activities to further investigate or minimize the risk so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Briviact. Potential risks are concerns for which an association with the use of this medicine is possible, based on available data, but such as association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 2–1: List of important risks and missing information

Important identified risks	Suicidality (class label for anticonvulsant products)
Important potential risks	None
Missing information	Data during pregnancy and lactation Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients

2.2 Summary of important risks

Table 2–2: Summary of important risks

Important identified risk: Suicidality (class label for anticonvulsant products)	
Evidence for linking the risk to the medicine	Suicide-related events have been reported more often in people who have epilepsy compared with the general population.
Risk factors and risk groups	Common additional disorders in patients with epilepsy that increase the risk of suicide include depression and learning difficulties or disability. A small increased risk of suicide-related events has also been reported in patients with epilepsy taking antiepileptic drugs including Briviact.
Risk minimization measures	Routine risk minimization measures: Available by prescription only

Table 2–2: Summary of important risks

	Section 4.4, Special Warnings and Precautions for Use, of the Summary of Product Characteristics (SmPC; class wording) and Section 4.8, Undesirable Effects, of the SmPC Packaging: • The brivaracetam (BRV) oral tablet pack contains unit dose packaging (blister) that requires a sequential withdrawal of tablets, which could interfere with the accomplishment of suicidal thoughts. • Intravenous formulation is provided in vials containing BRV 50mg in total, and the administration will be performed by a healthcare professional and not the patient. • Oral solution is packaged in bottles with 300mL fill volumes with a concentration of BRV 10mg/mL. This corresponds to 3g of BRV if the entire volume is taken. Once placed, the adaptor for the 5 or 10mL oral-dosing syringe is difficult to remove, thus limiting the ability to drink significant volume. The oral solution, although flavored, does not have a pleasant taste due to the bitter tasting drug substance. Additional risk minimization measures: None
Missing information: Pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures: Available by prescription only Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy and North American Antiepileptic Drug Pregnancy Registry. Activities include provision of requested data from UCB to the registries and regular review of interim outputs from the registries. • The protocols include possible activities to follow-up the children.
Missing information: Long-term effects on growth, endocrine function or sexual maturation, neurodevelopment, and cognitive and psychomotor development in pediatric patients	
Risk minimization measures	Routine risk minimization measures: Available by prescription only Additional risk minimization measures: None

BRV=brivaracetam; SmPC=summary of product characteristics

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization of Briviact.

2.3.2 Other studies in postauthorization development plan

Additional pharmacovigilance activities include the following: European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) and North American AED Pregnancy Registry.

Purpose of the study: collect data on pregnancy. Prescribers and reporters of pregnancy cases are encouraged to register pregnant women exposed to AED into the EURAP and North American AED Pregnancy Registry. References to registries are included in the pregnancy follow-up letter, US Call Center script, and on information for Medical Science Liaisons.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no specific adverse event follow-up forms that are specific for brivaracetam.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

This annex is not applicable.