ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 05, pp.30697-30703, May, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

BRIVARACETAM: BRIEF CLINICAL PROFILE OF A NEW ANTIEPILEPTIC DRUG

***Parag Bhattacharya, M.D.**

Medical Services Department, Intas Pharmaceuticals Limited, Ahmedabad, India

ARTICLE INFO

Article History:
Received 27th February, 2016
Received in revised form
24th March, 2016
Accepted 26th April, 2016
Published online 10th May, 2016

Key words:
Epilepsy,
Antiepileptic Drugs,
Synaptic Vesicle Protein,
Partial-Onset Seizures,
Generalized Seizures,
Progressive Myoclonic Epilepsies,
Efficacy,
Safety.

ABSTRACT

Despite availability of several antiepileptic drugs (AEDs) for the management of epilepsy the problems of inadequate seizure control and disturbing side effects with these drugs persist and hence, quest continues for newer agents with superior clinical efficacy and safety profile. Brivaracetam (BRV) is a new AED that is an analog of levetiracetam (LEV). Its mechanism of antiseizure action seemingly involves selective binding to synaptic vesicle protein 2A, akin to LEV. Its safety and efficacy as an add-on therapy have been studied primarily in adult epilepsy patients with uncontrolled partial-onset seizures. In addition, a few studies have involved patients with generalized seizures, and progressive myoclonic epilepsies. BRV has been found to be efficacious and well tolerated as add-on therapy in partial-onset seizures and generalized seizures. Side effects due to BRV tend to be non-serious, mild-to-moderate in intensity and transient in nature. This article has described the brief pharmacological and clinical profile of BRV.

Citation: ***Parag Bhattacharya,*** **2016.** "Brivaracetam: brief clinical profile of a new antiepileptic drug", *International Journal of Current Research*, 8, (05), 30697-30703.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent and unpredictable episodes of seizure in which normal brain function is interrupted temporarily and various symptoms are produced as a consequence. Worldwide, millions suffer from epilepsy with significant morbidity and mortality. A plethora of antiepileptic drugs (AEDs) is presently available to treat epilepsy. Over a dozen second-generation AEDs have been introduced in the last 25 years. Overall, these have significantly improved the outlook management of epilepsy. However, the fact remains that approximately one-third of patients with epilepsy fail to achieve complete seizure control with existing treatments (Spencer, 2002; Schuele *et al*., 2008). In addition, currently available AEDs produce a wide range of adverse effects, some of which can be life threatening (Schuele *et al*., 2008; Zaccara *et al*., 2007). Thus, yet unmet clinical need for more efficacious AEDs with less risk of adverse effects has continued to drive the search for still newer agents with better efficacy and safety profile.

****Corresponding author: Parag Bhattacharya,***
Medical Services Department, Intas Pharmaceuticals Limited, Ahmedabad, India

Synaptic Vesicle Protein 2A as a Novel Target for Antiepileptic Drug Action

The major mechanisms of action of older AEDs include (1) inhibition of voltage-gated Na^+ or Ca^{2+} channels, (2) reduction in synaptic excitation mechanisms (typically via glutamate receptors), and (3) enhancement of synaptic inhibition (usually via gamma-aminobutyric acid (GABA) receptors) (Porter *et al*., 2012). Whereas, some recently introduced AEDs are known to produce anticonvulsant effect by completely novel mechanisms, e.g., levetiracetam (LEV) by binding to synaptic vesicle protein 2A (SV2A) (Lyseng-Williamson, 2011), retigabine by binding to and opening neuronal voltage-gated potassium channels (KCNQ2/3 and KCNQ3/5) (Plosker and Scott, 2006), and perampanelby producing selective, noncompetitive antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors on post-synaptic neurons (Plosker *et al*., 2012). While investigating the mechanism of action of LEV, it was observed that none of the commonly known mechanisms significantly contributed to its anticonvulsant effects. However, further research revealed that binding to SV2A correlated well with its anticonvulsant activity (Gillard *et al*., 2011).

Synaptic vesicle 2 (SV2) proteins are glycoproteins found in secretory vesicles in neural and endocrine cells in vertebrates (Buckley *et al*., 1985). They are integral membrane proteins with a structure similar to members of the large major facilitator superfamily (MFS) of transporters (Bajjalieh *et al*., 1992). Yet, they have not been shown to exhibit any transporting function. They are found in both synaptic vesicles and large dense core vesicles. SV2 exists in three isoforms in mammals: SV2A, SV2B, and SV2C. Of the three isoforms, SV2A is most ubiquitous and is expressed in all brain structures and in all types of neurons (Bajjalieh *et al*., 1994). The SV2A protein is located inside the presynaptic terminal of neurons within the membrane of synaptic vesicles.

Never before had an AED been known to bind inside neurons or to bind to a protein suggested to be directly involved in the molecular mechanism of exocytosis and neurotransmitter release. Thus, LEV was hypothesized to have a completely unique and nontraditional AED mechanism (Meehan, 2011).

BRIVARACETAM

Brivaracetam (BRV)((2S)-2-((4R)-2-oxo-4-propylpyrro-lidinyl) -butanamide; $C_{11}H_{20}N_2O_2$ = 212.29) is a structural analog of LEV, an AED binding to the SV2A within the presynaptic axon terminal and preventing release of neurotransmitters from synaptic vesicles to decrease excitability in hyperexcited neurons. Similar to LEV, BRV binds to SV2A in the brain but with 15- to 30-fold higher affinity and greater selectivity than LEV, as demonstrated in preclinical models (Gillard *et al*., 2011). While the exact role of SV2A is unknown, there is a high correlation between binding affinity at SV2A and antiepileptic activity (Gillard *et al*., 2011). In January 2016 oral BRV has been approved in the EU as an adjunctive treatment for partial-onset seizures with or without secondary generalization (spreading to both sides of the brain after the initial seizure) in patients aged ≥16 years, and is awaiting approval in the USA, Australia, Canada and Switzerland (Markham, 2016).

PHARMACODYNAMICS

BRV selectively bound to SV2A with 15 to 30-fold higher affinity than levetiracetam in an in-vitro study of its binding profile in rat, human and mouse brain, and to recombinant human SV2A expressed in Chinese hamster ovary (CHO) cells (Meehan, 2011). The drug reduced epileptiform responses in rat hippocampal slices ex-vivo (Matagne *et al*., 2008) and, in vivo, protected against electroshock and pentylenetetrazol-induced seizures in normal mice, and against secondarilygeneralized motor seizures in corneally kindled mice and hippocampal-kindled rats (Matagne *et al*., 2008). In amygdala-kindled rats, BRV significantly reduced seizure severity scores and- at the highest dose tested - the after-discharge duration (Matagne *et al*., 2008). BRV demonstrated greater protection against the expression of clonic convulsions than levetiracetam in audiogenic seizure-susceptible mice and more effectively suppressed spontaneous spike-and-wave discharges in Genetic Absence Epilepsy Rats from Strasbourg (Matagne *et al*., 2008). In an in vivo study in audiogenic mice, BRV crossed the blood-brain barrier more quickly than levetiracetam and had a faster onset of action against seizures (Zona *et al*., 2010). Physiologically based pharmacokinetic modelling of this data predicted considerably higher blood brain barrier permeability in humans for BRV than levetiracetam (0.315 and 0.015 ml/min/g brain). In a study in rhesus monkeys BRV entered the brain ≈7 times faster than levetiracetam after intravenous (IV) administration (Nicolas *et al*., 2016). In addition to SV2A block, BRV also exhibits inhibitory activity on neuronal voltage-gated sodium channels (VGSC) playing a role as a partial antagonist, as has been reported for other AEDs (Zona *et al*., 2010; Kohling, 2002).

PHARMACOKINETICS

The pharmacokinetic profile of BRV has been evaluated in healthy adult volunteers, the elderly, patients with epilepsy, and patients with hepatic or renal dysfunction (Sargentini-Maier *et al*., 2008; Sargentini-Maier *et al*., 2007; Rolan *et al*., 2008; Sargentini-Maier *et al*., 2012; Stockis *et al*., 2013). The drug exhibits favorable pharmacokinetic properties due to its linear and predictable profile, with low inter-subject variability and close to 100% bioavailability (Sargentini-Maier *et al*., 2008; Sargentini-Maier *et al*., 2007; Rolan *et al*., 2008). The pharmacokinetic differences in elderly patients, as compared to healthy volunteers, are not relevant and therefore dose adjustment does not seem to be required (Stockis *et al*., 2013). Following oral administration, BRV is quickly absorbed from the gastrointestinal tract with a linear and dose-dependent profile, and it is unaffected by the presence of food (Sargentini-Maier *et al*., 2007; von Rosenstiel *et al*., 2007). The median time to peak plasma concentration (T_{max}) for tablets taken without food is 1 hour (range 0.25 to 3 hours). Co-administration with a high-fat meal was found to slow absorption, but the extent of absorption remained unchanged. BRV is rapidly and evenly distributed in most tissues. The distribution volume is close to the total body water content (Vz =0.5 L/kg) and BRV is weakly bound (17.5%) to plasma proteins. Terminal half-life is approximately 8-9 hours and BRV is usually administered twice daily in equal doses (Ferlazzo *et al*., 2015). BRV is eliminated primarily by metabolism and by excretion in the urine. BRV is extensively metabolisedto three pharmacologically inactive compounds and more than 95% is excreted through the urine with an unchanged fraction of 8%-11% (Sargentini-Maier *et al*., 2008; Mumoli *et al*., 2015). The main metabolic pathway consists of the hydrolysis of BRV's acetamide group, leading to the formation of an acid metabolite (BRV-AC; 34.2% of the radiolabeled urinary dose) (Sargentini-Maier *et al*., 2008). A smaller proportion of the drug is converted by the cytochrome P450 2C19 (CYP2C19) **(**Stockis *et al*., 2014**)** into a hydroxy metabolite (BRV-OH; 15.9% of the urinary dose). From the participation of both of these pathways, a hydroxyacid metabolite is produced (15.2% of the dose in the urine) (Sargentini-Maier *et al*., 2008). In human subjects possessing genetic variations in CYP2C19, production of the hydroxy metabolite is decreased 2-fold or 10-fold, while the blood level of BRV itself is increased by 22% or 42%, respectively, in individuals with one or both mutated alleles. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. (BRIVIACT® Prescribing Information, 2016)

BRV is excreted mostly in the urine. More than 95% of the dose, including metabolites, is excreted in the urine within 72 hours after intake. Fecal excretion accounts for less than 1% of the dose. Less than 10% of the dose is excreted unchanged in the urine. Thirty-four percent of the dose is excreted as the carboxylic acid metabolite in urine. (BRIVIACT® Prescribing Information, 2016)

An open-label trial on patients with liver dysfunction revealed that the plasmatic half-life of BRV may increase up to 17.4 hours, depending on the severity of the hepatic disease. Nevertheless, the exposure to BRV increases by 50%-60% in patients with hepatic impairment, irrespective of the severity of the pathology, defined on the basis of the Child-Pugh score (Stockis *et al*., 2013; von Rosenstiel, 2007). Thus, according to such evidence, the maximum daily dose of BRV should be reduced by one-third in patients with liver disease (Stockis *et al*., 2013). The maximum recommended dosage of BRV in patients with hepatic impairment is 75 mg twice daily. (BRIVIACT® Prescribing Information, 2016) When exposed to a single 200 mg oral dose of BRV, patients with severe kidney dysfunction not requiring dialysis (creatinine clearance,15 mL/min) show a 10-fold decrement on renal excretion of the three metabolites, but it is not clear if adjustment of the dose is required (Sargentini-Maier *et al*., 2012).

CLINICAL EFFICACY IN EPILEPSY

Partial-onset Seizures

Efficacy and tolerability data of BRV as add-on therapy in adult patients with uncontrolled partial seizures are available from six (two phase II (French *et al*., 2010; Van Paesschen *et al*., 2013) and four phase III (Ryvlin *et al*., 2014; Biton *et al*., 2014; Kwan *et al*., 2014; Klein *et al*., 2015) randomized placebo-controlled clinical trials (Table 1) and two meta-analyses (Tian *et al*., 2015; Ma *et al*., 2015). Salient findings of the six studies are described here.

(1) French *et al*. (2010) (Table 1) This phase II study showed the efficacy of BRV (in terms of median percentage decrease in seizure frequency per week compared to placebo from the baseline) was related to the administered dose (ranging from 5-50 mg/day), but was statistically significant only for BRV 50 mg/day (9.8% for BRV 5 mg/day (*P*=0.240); 14.9% for BRV 20 mg/day (*P*=0.062); 22.1% for BRV 50 mg/day (*P*=0.004)). Seizure freedom rates during an observational treatment period of 7 weeks were 1.9% with placebo, 8.0% with BRV 5 mg/day, 7.7% with BRV 20 mg/day, and 7.7% with BRV at 50 mg/day.

(2) Van Paesschen *et al*. (2013) (Table 1) In this phase II btrial, 28 primary efficacy analysis did not reach statistical significance. In particular, the percent reduction in baseline-adjusted partial seizure frequency/week over placebo during the 7-week maintenance period over placebo was not significant in those treated with BRV 50 mg/day (14.7% reduction, *P*=0.093), or with BRV 150 mg/day (13.6% reduction, *P*=0.124).28 However, a significant difference over placebo for the same outcome measure was reported during the 10-week total treatment period for the BRV 50 mg/day group (17.7% reduction, *P*=0.026), as well as for the BRV 150 mg/day group (16.3% reduction, *P*=0.043). Seizure freedom was reached by a total of nine patients (five patients (9.4%) with BRV 50 mg/day; three patients (5.8%) with BRV 150 mg/day; and one patient (1.9%) with placebo).28

(3) Ryvlin *et al*. (2014) (Table 1) According to this study, BRV at a daily dose of 100 mg/day showed efficacy. The percentage reduction over placebo in the baseline-adjusted seizure frequency per week was 6.8% in those treated with BRV 20 mg/day (*P*=0.239), 6.5% in those treated with BRV 50 mg/day (*P*=0.261), and 11.7% in those treated with BRV 100 mg/day (*P*=0.037). Seizure freedom was achieved by two (2%) patients treated with BRV 20 mg/day, no patients who

Table 1. Randomized controlled trials for BRV

Study	Design	ITT Populationa	BRV Dose Range in mg/day	BRV Dose in mg/day and Clinical Responsevs. Placebo b	
				Responder Ratesc	Decrease in Seizure Frequencyd
French *et al*. (2010)	RCT, double-blind vs placebo	BRV: 154 P: 54	5-50	5: 32.0% 20: 44.2% 50: 55.8% P: 16.7%	5: 29.9% 20: 42.6% 50: 53.1%
Van Paesschen *et al*. (2013)	Do	BRV: 105 P: 52	50-150	50: 35.8% 150: 30.8% P: 17.3%	50: 34.9% 150: 28.3%
Ryvlin *et al*. (2014)	Do	BRV: 298 P: 100	20-100	20: 27.3% 50: 27.3% 100: 36.0% P: 20.0%	20: 30.0% 50: 26.8% 100:32.5%
Biton *et al*. (2014)	Do	BRV: 298 P: 98	5-50	5: 21.9% 20: 23.2% 50: 32.7% P: 16.7%	5: 20% 20: 22.5% 50: 30.5%
Kwan *et al*. (2014)	Do	BRV: 359 (POS 323; GS 36) P: 121 (POS 108; GS 13)	20-150e	30.3% (POS) 44.4% (GS) P: 16.7% (POS); 15.4% (GS)	26.9% (POS) 42.6% (GS)
Klein *et al*. (2015)	Do	BRV: 501 P: 209	100, 200f	100: 38.9% 200: 37.8% P: 21.6%	100: 22.8% 200: 23.2%

a. Intention-to-treat (ITT) population in BRV- (BRV) and placebo (P)-treated groups, respectively, b. In adult patients with refractory partial-onset seizures except where mentioned, c. Proportion of patients with ≥50% decrease in seizure frequency, d. Median percentage decrease in seizure frequency per week from baseline; data shown for BRV alone, e. Given in flexible doses f. Fixed doses

Abbreviations: RCT, randomized clinical trials; ITT, intention-to-treat; BRV, BRV; P, placebo; POS, partial-onset seizures, GS, generalized seizures

Adapted from: (1) Ferlazzo E, Russo E, Mumoli L, et al. Profile of BRV and its potential in the treatment of epilepsy.
Neuropsychiatr Dis Treatment 2015:11 2967-2973; and (2) Mumoli L, Palleria C, Gasparini S, et al.
BRV: review of its pharmacology and potential use as adjunctive therapy in patients with partial onset seizures.
Drug Des Devel Ther. 2015; 9:5719-5725.

Table 2. Most common adverse effects of BRV (BRV) in six randomized, placebo-controlled clinical trials

Trial	Side effects of BRVdose [a] versus placebo (P) observed in 6 clinical trials				
	Headache	Somnolence	Fatigue	Dizziness	Gastrointestinal disturbance
French *et al*. (2010)	5: 8% 20: 3.8% 50: 1.9% P: 7.4%	5: 2% 20: 5.8% 50: 5.8% P: 7.4%	5: 0% 20: 3.8% 50: 5.8% P: 3.7%	5: 2% 20: 0% 50: 7.7% P: 5.6%	NR
Van Paesschen *et al*. (2013)	50: 15.1% 150: 7.7% P: 7.7%	50: 9.4% 150: 5.8% P: 5.8%	50: 13.2% 150: 5.8% P: 7.7%	50: 3.8% 150: 9.6% P: 5.8%	50: 9.4% 150: 19.3% P: 15.3%
Ryvlin *et al*. (2014)	20: 14.1% 50: 18.2% 100: 9% P: 9%	20: 8.1% 50: 6.1% 100: 8% P: 6%	20: 3% 50: 4% 100: 8% P: 2%	20: 5.1% 50: 7.1% 100: 5% P: 8%	20: 0% 50: 1% 100: 6% P: 4%
Biton *et al*. (2014)	5: 11.3% 20: 6% 50: 13% P: 14.3%	5: 14.4% 20: 14% 50: 16.8% P: 7.1%	5: 3.1% 20: 13% 50: 9.9% P: 2%	5: 12.4% 20: 14% 50: 15.8% P: 9.2%	5: 11.3% 20: 12% 50: 16.8% P: 6.1%
Kwan *et al*. (2014)	14.2%[b] P: 19.8%	14.1%[b] P: 4.1%	7.8%[b] P: 4.1%	8.6%[b] P: 5.8%	5.6%[b] P: 8.3%
Klein *et al*. (2015)	100: 6.7% 200: 8.0% P: 8.4%	100: 19.4% 200: 16.8% P: 7.7%	100: 7.5% 200: 11.6% P: 3.8%	100: 10.3% 200: 14.4% P: 5%	NR

a. Daily doses of BRV are represented by numerals at left hand side of each column under the side effects
b. Side effects for flexibly dosed BRV
Abbreviations: NR, not reported; P, placebo.
Adapted from: (1) Ferlazzo E, Russo E, Mumoli L, et al. Profile of BRV and its potential in the treatment of epilepsy. Neuropsychiatr Dis Treatment 2015:11 2967-2973.

were treated with BRV 50 mg/day, four (4%) patients treated with BRV 100 mg/day, and no patients who were treated with the placebo.29

(4) Biton *et al*. (2014) (Table 1) The trial highlighted that BRV has a dose-related efficacy.30 In particular, the median reduction in the percentage over placebo from the baseline of seizure frequency per week was 0.9% (*P*=0.885) for BRV 5 mg/day, 4.1% (*P*=0.492) for BRV 20 mg/day, and 12.8% (*P*=0.025) for BRV 50 mg/day.30 Seizure freedom was reached by a total of six patients (no patients treated with the placebo, one (1.1%) patient treated with BRV 5 mg/day, one (1.1%) patient treated with in BRV 20 mg/day, and four (4.0%) patients treated with BRV 50 mg/day).

(5) Kwan *et al*. (2014) (Table 1) This trial tested BRV at individually-tailored doses ranging from 20-150 mg/day in patients suffering from either partial or generalized refractory seizures.31 The baseline-adjusted percentage reduction over placebo of the partial seizure frequency per week was not significant in patients with partial seizures (7.3%; *P*=0.125).31 Five (1.5%) patients with partial seizures were seizure free during the treatment period.

(6) Klein *et al*. (2015) (Table 1) The trial showed a significant efficacy of BRV at 100 and 200 mg/day, compared to placebo with a median percentage decrement over placebo in a 28-day adjusted seizure frequency of 22.8% when using BRV 100 mg/day (*P*,0.001), and of 23.2% when using BRV 200 mg/day (*P*,0.001). During the treatment period, 25 patients reached seizure freedom (two (0.8%) patients treated with placebo; 13 (5.2%) patients treated with BRV 100 mg/day (*P*=0.003 compared to placebo); and ten (4.0%) patients treated with BRV 200 mg/day (*P*=0.019 compared to placebo)). In five of these trials (French *et al*., 2010; Van Paesschen *et al*., 2013; Ryvlin *et al*., 2014; Biton *et al*., 2014; Kwan *et al*., 2014) the continuation of LEV was allowed.

It seems that patients with a concomitant use of LEV did not respond as well to BRV in comparison to the patients not currently taking LEV, suggesting that its concomitant use may decrease BRV efficacy. Due to the small number of patients taking LEV in these trials, further studies should be performed to evaluate this pharmacodynamic interaction (Tian *et al*., 2015).

Generalized Seizures

Data are available from a single published trial that has evaluated the efficacy of BRV in generalized seizures (Kwan *et al*., 2014). [(32)]In this study, 49 patients had generalized seizures, mostly tonic-clonic (30 patients), absences (14 patients), and myoclonic (14 patients).

Two (5.6%) patients with generalized seizures were seizure free during the treatment period. The number of generalized seizure days per week reduced from 1.42 at baseline to 0.63 in the BRV-treated patients (n=36), and from 1.47 at baseline to 1.26 in the placebo group (n=13) (Kwan *et al*., 2014). Further, the median percentage reduction from baseline in generalized seizure days per week was 42.6% in the BRV group versus 20.7% in the placebo group (statistical significance not shown).

Progressive Myoclonic Epilepsies

So far two trials (Kälviäinen *et al*., 2009) have evaluated the efficacy of BRV as an add-on therapy in Unverricht-Lundborg disease, the most frequent and less severe form of progressive myoclonic epilepsies (Magaudda *et al*., 2006). However, these studies did not report a significant improvement of myoclonus with BRV. Because of several study limitations including a small sample size and the unpredictable inter- and intra-subject variability of myoclonus in Unverricht-Lundborg disease, further studies in his condition are warranted.

Tolerability profile

BRV has been shown to have a favorable safety profile.Side effects reported in association with its administration are mild to moderate and usually do not affect patient compliance to the treatment. The most commonly reported adverse effects with BRV in adults were primarily related to the central nervous system and included headache, somnolence, fatigue, and dizziness (Table 2) (Sargentini-Maier *et al*., 2008). These adverse effects were mild to moderate in intensity and did not impair therapeutic compliance. Inone trial, the daily dose of BRV (20-150 mg) was well tolerated and associated with 6.1% of discontinuation rates due to ADRs compared to 5.0% of the placebo group (Kwan *et al*., 2014). ADRs induced by BRV appear to betime-related, which tend to disappearwith continued treatment. The sedative effects of BRV is dose-related in healthy men and appeared clearly from 600 mg upwards as a decrease in attention, motor control, and alertness (Sargentini-Maier *et al*., 2008).

Moreover, the type and the severity of ADRs are not influenced by food (Sargentini-Maier *et al*., 2008). Twice-daily administration of BRV reduces the peak-to-trough fluctuations of plasma concentrations and minimizes the adverse reactions, as observed in healthy males (Sargentini-Maier *et al*., 2008). No effects on cardiac function were reported even at very high daily dosages (up to 800 mg/d) (Rosillon *et al*., 2008). Data on the effect of BRV on humanfertility and teratogenic potential are currently not available. However, in animals, no adverse effects were detected up to the highest tested oral dose of 400 mg/kg/d on fertility, and no effects on pregnancy or fetal development at 600 mg/d were observed. (vonRosenstiel, 2007) Seizure aggravation or the appearance of new generalized seizures was rare: three studies reported this adverse event, occurring in similar proportions between placebo and treated group (4.3% vs 5.2%, *P*=0.67) (Ryvlin *et al*., 2014; Berkovic, 2014; Kwan *et al*., 2014). Further, a phase III study has been conducted to determine whether switching from levetiracetam to BRV reduces the incidence of nonpsychotic behavioral adverse events associated with the former (NCT01653262) (Yates *et al*., 2015). Physician-reported clinically meaningful reductions in behavioral adverse events were observed in 27 of 29(93.1 %) patients in the 12-week period after switching from levetiracetam to BRV (Yates *et al*., 2015).

Important Drug Interactions

Coadministration of BRV 200 mg once (study days 1 and 22) or twice daily (days 24 to 35) and carbamazepine(titrated to a dose of 300 mg twice daily on days 4-35) in volunteers (n = 14) did not significantly affect the area under the plasma concentration-time curve (AUC) of carbamazepine over a dosing interval, but was associated with a 2.6-fold increase in the AUC of the carbamazepine epoxide metabolite. The AUC of BRV decreased by 29 % and the hydroxy-BRV metabolite increased by 17% (Stockis *et al*., 2015). Coadministration of BRV 200 mg and ethanol to male volunteers (n = 18) was associated with additionaldeterioration in alcohol-associated psychomotor and cognitive impairment compared with ethanol alone (Stockis *et al*., 2015). BRV 100 mg/day had no clinically relevant effect on levonorgestrel or ethinylestradiol in female volunteers (n = 28) when coadministered with a combination oral contraceptive over five 28-day menstrual cycles (Stockis *et al*., 2014).

Conclusion

BRV is a novel AED whose efficacy and tolerability in partial epilepsies have been studied and established in six randomized controlled trials. (French *et al*., 2010; Van Paesschen *et al*., 2013; Ryvlin *et al*., 2014; Biton *et al*., 2014; Kwan *et al*., 2014; Klein *et al*., 2015) Two recent meta-analyses have also confirmed significant effects for BRV in patients with refractory partial seizures. (Tian *et al*., 2015; Ma *et al*., 2015) A wide range of BRV dosages has been evaluated in these trials (5-200 mg/day), but the most suitable dose for clinical use appears to be 50-100 mg/day. (Ferlazzo *et al*., 2015) The long-term efficacy and safety of BRV, its efficacy in generalized seizures, and suitability for mono therapy of seizures await further clinical evaluation.

Funding: None

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

Bajjalieh, S.M., Frantz, G.D., Weimann, J.M., McConnell, S.K., Scheller, R.H. 1994. Differential expression of synaptic vesicle protein 2 (SV2) isoforms. *J Neurosci*., 14:5223-5235.

Bajjalieh, S.M., Peterson, K., Shinghal, R., Scheller, R.H. SV2, 1992. a brain synaptic vesicle protein homologous to bacterial transporters. *Science*;257:1271-1273.

Biton, V., Berkovic, S.F., Abou-Khalil, B., Sperling, M.R., Johnson, M.E. and Lu, S. 2014. BRV as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. *Epilepsia*, 55(1):57-66.

BRIVIACT® Prescribing Information. UCB, Inc., Smyrna, GA 30080, 2016.

Buckley, K. and Kelly, R.B. 1985. Identification of a transmembrane glycoprotein specific for secretory vesicles of neural and endocrine cells. *J Cell Biol*., 100:1284-1294.

Ferlazzo, E., Russo, E., Mumoli, L., Sueri, C., Gasparini,. S, Palleria C. *et al*. Profile of BRV and its potential in the treatment of epilepsy. *Neuropsychiatr Dis Treatment*, 2015:11 2967-2973

French, J.A., Costantini, C., Brodsky, A., von Rosenstiel, P. and Group, N.S. 2010. Adjunctive BRV for refractory partial-onset seizures: a randomized, controlled trial. *Neurology*, 75(6):519-525.

Gillard, M., Fuks, B., Leclercq, K. *et al*. 2011. Binding characteristics of BRV, a selective, high affinity SV2A ligand in rat, mouseand human brain: relationship to anti-convulsant properties.*Eur J Pharmacol*., 664(1):36-44.

Kälviäinen, G., Genton, P. and Andermann, E. *et al*. Brivaracetm in patients with Unverricht-Lundborg Disease: results from two randomized, placebo-controlled, double-blind studies. In: Epilepsia Conference Proceedings: 28th

International Epilepsy Congress; June 28-July 2, 2009; Budapest. Abstract.

Klein, P., Schiemann, J. and Sperling, M.R. *et al*. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive BRV in adult patients with uncontrolled partial-onset seizures. *Epilepsia*. Epub 2015 Oct 16.

Kohling, R. 2002. Voltage-gated sodium channels in epilepsy. *Epilepsia*.;43(11):1278-1295.

Kwan, P., Trinka, E., Van Paesschen, W., Rektor, I., Johnson, M.E., Lu, S. 2014. Adjunctive BRV for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. *Epilepsia*., 55(1):38-46.

Lyseng-Williamson, K.A. 2011. Levetiracetam - a review of its use in epilepsy. *Drugs*; 71 (4): 489-514

Ma, J., Huang, S. and You, C. 2015. Adjunctive BRV for patients with refractory partial seizures: a meta-analysis of randomized placebo-controlled trials. *Epilepsy Res*., 114:59-65.

Magaudda, A., Ferlazzo, E., Nguyen, V.H. and Genton, P. 2006. Unverricht-Lundborg disease, a condition with self-limited progression: long-term follow-up of 20 patients. *Epilepsia*., 47(5):860-866.

Markham A. BRV: First Global Approval. *Drugs*. DOI 10.1007/s40265-016-0555-6, Published online: 22 Feb 2016

Matagne, A., Margineanu, D.G., Kenda, B. *et al*. 2008. Anti-convulsive and anti-epileptic properties of BRV (ucb 34714), a high affinity ligand for the synaptic vesicle protein, SV2A. *Br J Pharmacol*., 154(8):1662-71.

Meehan, A.L. Identifying the mechanism of action of the antiepileptic drug levetiracetam in synaptic vesicle release and its implications for epilepsy - A dissertation submitted to the Faculty of the Graduate School of the University of Minnesota. 2011 July.

Mumoli, L., Palleria, C., Gasparini, S., Citraro, R., Labate, A., Ferlazzo, E. *et al*. 2015. BRV: review of its pharmacology and potential use as adjunctive therapy in patients with partial onset seizures. *Drug Des DevelTher*., 9:5719-5725.

Nicolas, J.M., Hannestad, J., Holden, D. *et al*. 2016. BRV, a selective high-affinity synaptic vesicle protein 2A (SV2A) ligand with preclinical evidence of high brain permeability and fast onset of action. *Epilepsia*., 57(2):201-9.

Plosker, G.L. 2012. Perampanel - as adjunctive therapy in patients with partial-onset seizures. *CNS Drugs*; 26:1085-1096

Plosker, G.L., Scott, L.J. 2006. Retigabine: in partial seizures. *CNS Drugs*, 20 (7): 601-8.

Porter, R.J., Dhir, A., Macdonald, R.L., Rogawski, M.A. 2012. Chapter 39: Mechanisms of action of antiseizure drugs. In, Handbook of Clinical Neurology, Vol. 108 (3rd series) Epilepsy, Part II, H. Stefan and W.H. Theodore, Editors, Elsevier B.V. pp 663-681

Rolan, P., Sargentini-Maier, M.L., Pigeolet, E. and Stockis, A. The pharmacokinetics, CNS pharmacodynamics and adverse event profile of BRV after multiple increasing oral doses in healthy men. *Br J ClinPharmacol*., 2008;66(1):71-75.

Rosillon, D., Astruc, B., Hulhoven, R. *et al*. 2008. Effect of BRV on cardiac repolarisation – a thorough QT study. *Curr Med Res Opin*., 24(8):2327–2337.

Ryvlin, P., Werhahn, K.J., Blaszczyk, B., Johnson, M.E. and Lu, S. 2014. Adjunctive BRV in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. *Epilepsia*., 55(1):47-56.

Sargentini-Maier, M.L., Espie, P., Coquette, A. and Stockis, A. 2008. Pharmacokinetics and metabolism of 14C-BRV, a novel SV2A ligand, in healthy subjects. *Drug MetabDispos*., 36(1):36-45.

Sargentini-Maier, M.L., Rolan, P. and Connell, J. *et al*. 2007. The pharmacokinetics, CNS pharmacodynamics and adverse event profile of BRV after single increasing oral doses in healthy males. *Br J ClinPharmacol*., 63(6):680-688.

Sargentini-Maier, M.L., Sokalski, A., Boulanger, P., Jacobs, T. and Stockis, A. 2012. BRV disposition in renal impairment. *J ClinPharmacol*., 52(12):1927-1933.

Schuele, S.U., Lu¨ ders H.O. 2008. Intractable epilepsy: management and therapeutic alternatives. *Lancet Neurol*., 7: 514-24

Spencer, S.S. 2002. When should temporal-lobe epilepsy be treated surgically? *Lancet Neurol*.,1: 375-82

Stockis, A., Chanteux, H., Rosa, M., *et al*. 2015. BRV and carbamazepine interaction in healthy subjects and in vitro. *Epilepsy Res*.;113:19-27.

Stockis, A., Kruithof, A.C., Van Gerven, J.M. *et al*. 2015. Interaction study between BRV and ethanol in healthy subjects (abstract no. 2.307). *Epilepsy Curr*., 15(Suppl 1):332.

Stockis, A., Sargentini-Maier, M.L., Horsmans, Y. 2013. BRV disposition in mild to severe hepatic impairment. *J ClinPharmacol*., 53(6):633-641.

Stockis, A., Watanabe, S., Fauchoux, N. 2014. Interaction between BRV (100 mg/day) and a combination oral contraceptive: a randomized, double-blind, placebo-controlled study. *Epilepsia*., 55(3):e27-31.

Stockis, A., Watanabe, S., Rouits, E., Matsuguma, K. and Irie, S. BRV single and multiple rising oral dose study in healthy Japanese participants: influence of CYP2C19 genotype. *Drug MetabPharmacokinet*., 2014;29(5):394-399.

Tian, X., Yuan, M., Zhou, Q. and Wang, X. 2015. The efficacy and safety of BRV at different doses for partial-onset epilepsy: a meta-analysis of placebo-controlled studies. *Expert Opinion on Pharmacotherapy*, 16(12):1755-1767.

Van Paesschen, W., Hirsch, E., Johnson, M., Falter, U., von Rosenstiel, P. 2013. Efficacy and tolerability of adjunctive BRV in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. *Epilepsia*., 54(1):89-97.

vonRosenstiel, P. BRV (UCB 34714). *Neurotherapeutics*. 2007;4(1):84-87.

Yates, S.L., Fakhoury, T., Liang, W. *et al*. 2015. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to BRV. *Epilepsy Behav*., 52:165-8.

Zaccara, G., Franciotta, D. and Perucca, E. 2007. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia*., 48: 1223-44

Zona, C., Pieri, M., Carunchio, I., Curcio, L., Klitgaard, H., Margineanu, D.G. 2010. BRV (ucb 34714) inhibits Na(+) current in rat cortical neurons in culture. *Epilepsy Res*., 88(1):46-54.

****