Taiwan Food and Drug Administration

Assessment Report

Trade Name：
必治癲膜衣錠 10 毫克, 25 毫克, 50 毫克, 100 毫克
必治癲口服溶液 10 毫克/毫升
必治癲注射液 10 毫克/毫升
Briviact Tablets 10mg, 25mg, 50mg, 100mg
Briviact Oral Solution 10mg/ml
Briviact Solution for Injection 10mg/ml

Active Ingredient：Brivaracetam

License Number:
衛部藥輸 027714 號
衛部藥輸 027715 號
衛部藥輸 027716 號
衛部藥輸 027717 號
衛部藥輸 027719 號
衛部藥輸 027718 號

Applicant：台灣優時比貿易有限公司

Approval Date： 108.8.23

Indication：
BRIVIACT 適用於 4 歲以上局部發作的癲癇患者的治療。
(4 歲以上有或無次發性全身發作的局部發作癲癇患者的單一藥物治療或輔助治療。)

因尚未確立兒童患者使用 **BRIVIACT** 注射液的安全性。**BRIVIACT** 注射液適用於成人**(16** 歲及以上**)**局部發作的癲癇患者的治療。

BRIVIACT is indicated for the treatment of partial-onset seizures in patients 4 years of age and older.

As the safety of BRIVIACT injection in pediatric patients has not been established, BRIVIACT injection is indicated for the treatment of partial-onset seizures only in adult patients (16 years of age and older).

1. **Background Information**

<table>
<tr><td>Trade Name</td><td>Briviact Tablets 10mg, 25mg, 50mg, 100mg
Briviact Oral Solution 10mg/ml
Briviact Solution for Injection 10mg/ml</td></tr>
<tr><td>Active Ingredient(s)</td><td>Brivaracetam</td></tr>
<tr><td>Applicant</td><td>台灣優時比貿易有限公司</td></tr>
<tr><td>Dosage Form & Strengths</td><td>Tablets 10mg, 25mg, 50mg, 100mg
Oral Solution 10mg/ml
Solution for Injection 10mg/ml</td></tr>
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因尚未確立兒童患者使用 BRIVIACT 注射液的安全性。BRIVIACT 注射液適用於成人(16 歲及以上)局部發作的癲癇患者的治療。

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<tr><td>Posology</td><td><u>單一療法或輔助療法</u>
表 1 為成人患者與 4 歲以上的患者建議的劑量，4 歲至未滿 16 歲之兒童患者的建議劑量是依體重來投與，且只建議用口服投與。初始治療時，不需逐步調高劑量。應根據個別患者的耐受性與臨床反應來調整劑量。
表 1: 成年與 4 歲以上兒童病患的建議劑量
<table>
<tr><td>年齡與體重</td><td>初始劑量</td><td>最低與最高的維持劑量</td></tr>
<tr><td>成人(16 歲與以上)</td><td>每天 2 次,每次 50 毫克
(每天 100 毫克)</td><td>每天 2 次,每次 25-100 毫克
(每天 50-200 毫克)</td></tr>
<tr><td>體重 50 公斤或以上的兒</td><td>每天 2 次,每次 25-50 毫克（每</td><td>每天 2 次,每次 25-100 毫克</td></tr>
</table>
</td></tr>
</table>

科患者	天 50-100 毫克）	（每天 50-200 毫克）
體重 20-50 公斤的兒科患者	每天 2 次,每次 0.5-1 毫克/公斤（每天 1-2 毫克/公斤）	每天 2 次,每次 0.5-2 毫克/公斤（每天 1-4 毫克/公斤）
體重 11-20 公斤的兒科患者	每天 2 次,每次 0.5-1.25 毫克/公斤（每天 1-2.5 毫克/公斤）	每天 2 次,每次 0.5-2.5 毫克/公斤（每天 1-5 毫克/公斤）

成人(16 歲或以上)的患者使用 BRIVIACT 注射液的劑量

初始治療時,不需逐步調高劑量。建議的起始劑量為 50 mg 每日 2 次(每日 100 mg)。根據個別患者的耐受性與反應，可將劑量調降為 25 mg 每日 2 次(每日 50 mg)或調高為 100 mg 每日 2 次(每日 200 mg) [請參閱臨床試驗(14)]。

當成人患者暫時無法以口服給藥時，可使用 BRIVIACT 注射液給藥[請參閱 2.3 段 BRIVIACT 注射液的配製與給藥方法]。BRIVIACT 注射液應以靜脈注射的方式給於成人患者，其劑量和頻率應與 BRIVIACT 錠劑及口服液劑相同。尚無兒童患者使用 BRIVIACT 注射液的臨床研究。
BRIVIACT 注射液的臨床試驗經驗僅限於連續 4 天的治療。

Monotherapy or Adjunctive Therapy

The recommended dosage for adults and pediatric patients 4 years of age and older is included in Table 1. In pediatric patients 4 years to less than 16 years of age, the recommended dosing regimen is dependent upon body weight and is only recommended to be administered orally. When initiating treatment, gradual dose escalation is not required. Dosage should be adjusted based on clinical response and tolerability.

Table 1: Recommended Dosage for Adults and Pediatric Patients 4 Years and Older

Age and Body Weight	**Initial Dosage**	**Minimum and Maximum Maintenance Dosage**
Adults (16 years and older)	50 mg twice daily (100 mg per day)	25 mg to 100 mg twice daily

<table>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>(50 to 200 mg per day)</td></tr>
<tr><td>Pediatric patients weighing 50 kg or more</td><td>25 mg to 50 mg twice daily (50mg to 100 mg per day)</td><td>25 mg to 100 mg twice daily (50 to 200 mg per day)</td></tr>
<tr><td>Pediatric patients weighing 20 kg to less than 50 kg</td><td>0.5 mg/kg to 1 mg/kg twice daily (1 mg/kg to 2 mg/kg per day)</td><td>0.5 mg/kg to 2 mg/kg twice daily (1 mg/kg to 4 mg/kg per day)</td></tr>
<tr><td>Pediatric patients weighing 11 kg to less than 20 kg</td><td>0.5 mg/kg to 1.25 mg/kg twice daily (1 mg/kg to 2.5 mg/kg per day)</td><td>0.5 mg/kg to 2.5 mg/kg twice daily (1 mg/kg to 5 mg/kg per day)</td></tr>
</table>

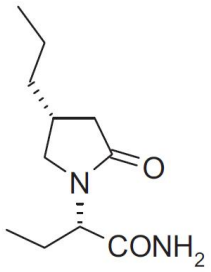
<u>BRIVIACT Injection Dosage in Adult Patients (16 years and older)</u>
BRIVIACT injection may be used for adult patients when oral administration is temporarily not feasible [see Dosage and Administration (2.3)]. BRIVIACT injection should be administered intravenously to adult patients at the same dosage and same frequency as BRIVIACT tablets and oral solution. The use of BRIVIACT injection in pediatric patients has not been studied.
The clinical study experience with BRIVIACT injection is limited to 4 consecutive days of treatment.
</td></tr>
<tr><td>Pharmacological Category
ATC Code</td><td>N03AX23</td></tr>
</table>

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, brivaracetam, is chemically designated as (2*S*)-2-[(4*R*)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide and has the following structure:



It is a white to off-white crystalline powder. The molecular formula and the molecular weight are $C_{11}H_{20}N_2O_2$ and 212.29 g/mol, respectively. It is not hygroscopic. It is very soluble in water.

Adequate information of characterization of the drug substance has been provided. The structure of brivaracetam is confirmed by elemental analysis, UV spectrum, IR spectrum, mass spectrum, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR) and X-ray crystallography.

The specification includes tests for appearance, identification, assay, impurities, stereoisomeric impurities, residual solvents, water content, heavy metals, catalyst content, residue on ignition, microbial limits, particle size (oral grade only) and bacterial endotoxins (injectable grade only).

2.1.2 Drug product

Brivaracetam drug products are supplied as the following dosage forms: tablets, oral solution and solution for injection. Brivaracetam tablets are colored, debossed 10 mg, 25 mg, 50 mg and 100 mg tablets packaged in blisters. Brivaracetam oral solution is a slightly viscous, clear, colorless to yellowish liquid containing brivaracetam in solution at a concentration of 10 mg/mL packaged in an amber glass bottle. Brivaracetam solution for injection is a clear, colorless, sterile, preservative-free solution packaged in a single-use glass vial. Each single-use vial contains 50 mg of brivaracetam in solution, at a concentration of 10 mg/mL. All excipients used in the drug product formulations are well known pharmaceutical ingredients used in pharmaceutical products and their quality is compliant with either compendial monographs or in-house standards.

Adequate release specifications have been presented for the brivaracetam dosage forms. The release specifications for brivaracetam tablets include tests for

appearance, identification, assay, degradation products, water content, uniformity of dosage units and disintegration. The release specification for brivaracetam oral solution includes tests for appearance, identification, identification of preservative, relative density, pH, degradation products, assay of active substance, assay of preservative and microbial limits. The release specification for brivaracetam solution for injection includes tests for appearance, identification, assay, degradation products, pH, osmolality, sterility, bacterial endotoxins, particulate contamination, extractable volume and container closure integrity. The analytical methods are adequately described and non-compendial methods are appropriately validated.

Stability data on brivaracetam dosage forms stored under long term conditions (25°C/60% RH, 30°C/65% RH or 30°C/75% RH) and accelerated conditions (40°C/75% RH) is provided. All results remain within specification throughout the studies indicating the products are stable over the stability study periods.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Brivaracetam (BRV) displayed a high and selectively affinity for SV2A in the brain. BRV was active in variety of animal seizure models, with a profile similar to LEV but with greater potency. BRV has very low clinically relevant safety concerns on cardiovascular, pulmonary, or gastrointestinal systems.

2.2.1 Toxicological Studies

The major findings in the pivotal repeat dose toxicity studies with BRV were changes in the liver (all species) and the kidney (male rats), which were either adaptive liver changes or species specific response, with low risk of human biological relevant. Brivaracetam (BRV) is unlikely to pose a genotoxic hazard. Long term carcinogenicity studies with BRV, a statistical significance increased incidence of liver tumors (hepatocellular adenoma and carcinoma) and thymus tumors (benign thymoma) were seen in male mice and in female rats, respectively. These tumor types observed in rodents, with uncertain clinical significance, but were considered to be limited. With regards to the reproductive and developmental toxicity studies, apart from adverse effects on development (increased post-implantation loss, reduced fetal bodyweight, and increased incidence of runted fetuses) due to maternal toxic in the pregnant rabbits at the highest dose tested during the period of organogenesis as well as findings in the F_1 pups consisted primarily of decreased in body weight with associated slight delayed sexual maturation (female), and lower motor activity at the highest dose tested in the PPND study in pregnant rats, no evidence of other apparent toxicity for reproductive developmental

parameters (including teratogenicity) were observed.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Brivaracetam is highly permeable and is rapidly and almost completely absorbed after oral administration. PK is dose-proportional from 10 to 600 mg. A high fat meal delayed T_{max} (median 3 h) and reduced C_{max} 30-40% while AUC was unchanged. Three dosage forms (tablet, oral solution and IV injection) show the same AUC, while the maximum plasma concentration is slightly higher after intravenous administration.

The plasma protein binding of brivaracetam was found to be low (≤ 20%) in both *in vitro* and *ex-vivo* human studies and independent of concentration. The blood-to-plasma ratio ranged between 0.83 - 0.90. The volume of distribution is 0.5 L/kg, a value close to that of the total body water. Brivaracetam is rapidly and evenly distributed in most tissues.

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid (approximately 60 % the elimination), and secondarily by hydroxylation on the propyl side chain (approximately 30 % the elimination). The hydrolysis of the amide moiety leading to the carboxylic acid metabolite (34 % of the dose in urine) is supported by hepatic and extra-hepatic amidase. *In vitro*, the hydroxylation of brivaracetam is mediated primarily by CYP2C19. Both metabolites are further metabolized forming a common hydroxylated acid formed predominantly by hydroxylation of the propyl side chain on the carboxylic acid metabolite (mainly by CYP2C9). *In vivo*, in human subjects possessing ineffective mutations of CYP2C19, production of the hydroxy metabolite is decreased 10-fold while brivaracetam itself is increased by 22 % or 42 % in individuals with one or both mutated alleles. The three metabolites are not pharmacologically active.

Brivaracetam is eliminated primarily by metabolism and by excretion 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. 34% of the dose is excreted as the carboxylic acid metabolite in urine. The terminal plasma half-life ($t_{1/2}$) is approximately 9 hours.

2.3.2 Interaction Studies

Based on *in vitro* data, brivaracetam did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, or 3A4. Brivaracetam weakly inhibited CYP2C19 and would not be expected to cause significant inhibition of CYP2C19 in humans. Brivaracetam was an inhibitor of epoxide hydrolase, (IC_{50} = 8.2 μM), suggesting that brivaracetam can inhibit the enzyme *in vivo*.

Based on *in vitro* data also demonstrated that brivaracetam will not induce CYP1A2, 2B6, 2C9, 2C19, 3A4, and epoxide hydrolase and will not inhibit BCRP, BSEP, MATE1, MATE2/K, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or P-gp *in vivo*.

The pharmacokinetic of brivaracetam is similar when used as monotherapy or an

adjunctive therapy for the treatment of partial onset seizures. Co-administration with rifampin decreases brivaracetam plasma concentrations by 45%, an effect that is probably the result of CYP2C19 induction.

2.3.3 Special Populations

There were no significant differences observed in the pharmacokinetics of brivaracetam based on gender and elderly. The dosage in pediatric patients is determined to match the similar exposure in adult patients.

A study in adult subjects with severe renal impairment (creatinine clearance<30 mL/min/1.73m^2 and not requiring dialysis) revealed that the plasma AUC of brivaracetam was increased (21%) relative to healthy controls, while the AUC of the acid, hydroxy, and hydroxyacid metabolites were increased 3-, 4-, and 21-fold, respectively. Due to the hydroxyacid metabolite did not reveal any safety concerns in non-clinical studies; no dose adjustment for renal impairments patients is required. Brivaracetam has not been studied in patients undergoing hemodialysis

A pharmacokinetic study in adult subjects with hepatic cirrhosis, Child-Pugh grades A, B, and C, showed 50%, 57%, and 59% increases in brivaracetam exposure, respectively, compared to matched healthy controls. Therefore, dose adjustment for hepatic impairments patients is required.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Three Phase 3, randomized, double-blind, placebo-controlled, pivotal studies (N01252, N01253, and N01358) evaluated the efficacy and safety of twice-daily oral administration of BRV 5 mg/day to 200 mg/day in adults (≥16 years) with refractory partial-onset seizures (POS) with or without secondary generalization. Study N01252 and Study No1253 were of identical design except for studying different dose range of BRV (Study N01252: 20 mg/day, 50 mg/day, and 100 mg/day; Study N01253: 5 mg/day, 20 mg/day, and 50 mg/day). Study N01358 was initiated after the completion of N01252 and N01253. The study recruited more subjects, investigating higher dose of BRV (100 mg/day and 200 mg/day). As well, it excluded subjects concomitant using of LEV or having taken LEV within 90 days prior to visit 1. The primary efficacy variable in both Study N01252 and Study N01253 was the POS (Type 1) frequency per week over the 12 week treatment period. That in Study N01358 was the POS (type 1) frequency per 28 days during 12-week treatment period. In both Study N01252 and Study N01253, the log-transformed POS frequency per week over the treatment per week [log(x+1)] was analyzed applying an ANCOVA model, including treatment and a stratification effect combining study region and concomitant LEV use as factors and the log-transformed baseline seizure frequency per week as covariate. In Study N01358, the primary analysis the USA was based on ANCOVA with log-transformed [log(x+1)] treatment period 28-day adjusted POS frequency as the outcome and an effect for

treatment, an effect for country, and an effect for the 4 combination of levels for LEV status and number of previous AEDs (≤2 vs. >2), and log-transformed baseline POS frequency as a continuous covariate. The primary outcome for the EU was the 50% responder rate based on percent reduction in POS frequency from baseline to the treatment period. The analysis of 50% responder outcome was based on a logistic regression model with an effect for treatment, an effect for country, and an effect for the 4 combination of levels for LEV status and number of previous AEDs (≤2 vs. >2), and log-transformed baseline POS frequency as a continuous covariate.

In Study N01252, the BRV 50 mg/day group showed a reduction in log-transformed POS frequency per week of 6.5% over PBO (p=0.261). The primary outcome did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.05 level for BRV 50 mg/day versus PBO prior to the testing of BRV 100 mg/day and BRV 20 mg/day in sequence. The comparison of BRV 100 mg/day versus PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome (p=0.037).

In Study N01253, the percent reductions over PBO in the POS frequency per week over the treatment period were -0.9%, 4.1%, and 12.8% in the BRV 5 mg/day, BRV 20 mg/day, and BRV 50 mg/day groups, respectively. The primary outcome achieved statistical significance for BRV 50 mg/day versus PBO (p=0.025). However, neither BRV 20 mg/day versus PBO nor BRV 5 mg/day versus PBO reached statistical significance based on the sequential testing procedure.

In Study No1358, the primary efficacy outcome for the USA was the percent reduction in POS (Type 1) frequency over PBO based on ANCOVA. The reductions in both BRV groups were statistically significant (p<0.001). The percent reduction in the 28-day adjusted POS frequency over PBO in the BRV 100 mg/day and 200 mg/day was similar (22.8% and 23.2%, respectively) with no dose response.

In summary, the 3 pivotal studies provided adequate evidence to support the efficacy of BRV 100 mg/day and BRV 200 mg/day for the treatment of partial-onset seizures in patients 16 years of age and older.

Efficacy of monotherapy was demonstrated by conversion-to-monotherapy trials, N01276 and N01306. The K-M predicted exit rate for BRV 50 mg/day at Day 112 was 0.487 (95% CI: 0.347, 0.626) in Study N01276 and 0.474 (95% CI: 0.310, 0.638) in Study N01306; the lower bounds were lower than historical control 0.722 (French et al, 2005).

Efficacy of oral solution and IV solution was established by BE studies to tablets.

Efficacy for pediatric population was supported by Studies N01263 and N01266 and population PK.

2.4.2 Safety Results

Major safety concerns are somnolence, dizziness, headache, irritability, depression/suicide, cognitive impairment, fatigue and elevated TG. Additional adverse events for pediatric population include vomiting, diarrhea and pyrexia. Rash and dysgeusia were additionally noted in IV injection.

2.5 Bridging Study Evaluation

After a single oral administration of 50 mg dose, the C_{max} and AUC_t of brivaracetam in healthy Japanese subjects were 1.16-fold and 1.24-fold to healthy non-Japanese subjects. After multiple oral 50 mg BID, the $C_{max,ss}$ and $AUC_{t,ss}$ of brivaracetam in healthy Japanese subjects were 1.40-fold and 1.01-fold to healthy non-Japanese subjects. Brivaracetam PK did not show difference between healthy subjects and target population. The exposure of brivaracetam in Asian target patient (2.6% in the anlaysis) was similar to non-Asian patient (less than 3% difference) at the 50 mg BID and 100 mg BID in population PK analysis.

At the single IV injection (2-minute infusion) 100 mg, the C_{max} and AUC_t of brivaracetam in healthy Japanese subjects were 2.31-fold and 1.20-fold to healthy non-Japanese subjects. Although the C_{max} was 2.3 folds higher in Japanese, the value of concentration did not higher than the value after single oral 1000 mg (single dose MTD) or oral 400 mg BID (not reach multiple dose MTD).

Considering the inter-subject variation of brivaracetam is about 30%, brivaracetam is none to minimally ethnically sensitive from PK aspect.

Consistent efficacy trend was found in 57 East Asian subgroup in Study N01358 (ITT=760). Rates of somnolence and dizziness were higher for East Asian subgroup in pooled dataset of Studies N01358 and N01254. For IV preparation, PK study in healthy volunteers revealed higher incidence of nausea (8.3% vs. 0%), dizziness (37.5% vs. 36.0%) and somnolence (54.2% vs. 4.0%) in Japanese as compared to Caucasians. Due to limited East Asian subjects currently, bridging study was waived with the condition that the sponsor should provide complete study reports of N01125, EP0083, EP0085, N01379, and EP0118 once available, all these studies were conducted in East Asia.

2.6 Conclusion

Approval of Briviact is recommended.

3. Post-Marketing Requirements

The sponsor should provide complete study reports of N01125, EP0083, EP0085, N01379, and EP0118 once available.