SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Zurzuvae 20 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg zuranolone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Size 1 hard capsules with a light-orange cap and an ivory to light-yellow body, printed with “S-217 20mg” in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zurzuvae is indicated for the treatment of moderate or severe postnatal depression (PND) in adults following childbirth (see section 5.1).

4.2 Posology and method of administration

Posology

Treatment should be initiated under the supervision of a specialist prescriber.

The recommended dose of zuranolone is 50 mg (two 25 mg capsules) for 14 days as a single course of treatment.

The dose of zuranolone may be reduced to 40 mg (two 20 mg capsules) if the patient does not tolerate 50 mg (see section 4.4).

Treatment duration beyond 14 days has not been evaluated.

If a patient forgets to take zuranolone, the patient should be instructed to skip the missed dose and take the next dose at their regular time the next day. The patient should not take additional capsules on the same day to make up for the missed dose.

Zuranolone may be used alone or as an adjunct to oral antidepressant therapy.

If dose discontinuation is required, treatment may be stopped without down-titration.

Special populations

Renal impairment
The recommended dose in patients with moderate (estimated glomerular filtration rate [eGFR] 30 to 59 mL/min) or severe renal impairment (eGFR < 30 mL/min not requiring dialysis) is 30 mg. No dose adjustment is necessary in patients with mild renal impairment (eGFR 60 to 89 mL/min) (see section 5.2).

Hepatic impairment
The recommended dose in patients with severe hepatic impairment (Child-Pugh class C) is 30 mg. No dose adjustment is necessary in patients with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B) (see section 5.2).

Concomitant use with CYP3A inhibitors
The recommended dose is 30 mg when used with strong CYP3A inhibitors (see section 4.5). No dose adjustment is recommended when zuranolone is concomitantly used with a moderate or weak CYP3A inhibitor e.g. fluoxetine.

Concomitant use with CYP3A inducers
Concomitant use of zuranolone with CYP3A inducers should be avoided (section 4.5).

Paediatric population
The safety and efficacy of zuranolone in postpubertal females less than 18 years old have not been established. No data are available.

There is no relevant use of zuranolone in prepubertal females.

Method of administration

Zuranolone should be taken orally once daily, in the evening with fat-containing food (e.g., nuts, peanut butter, avocado, eggs, and cheese) (see section 5.2).

Zuranolone capsules are swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- During pregnancy.

4.4 Special warnings and precautions for use

Impaired ability to drive or engage in potentially hazardous activities

Zuranolone impairs the ability to drive due to central nervous system (CNS) depressant effects. Patients should be counselled not to drive or engage in other potentially hazardous activities until at least 12 hours after taking each dose of zuranolone. Patients should be advised that they may not be able to assess their own ability to perform these activities (see section 4.7).

Central nervous system depressant effects

Zuranolone can cause CNS depressant effects such as somnolence and sedation (see section 4.8). Alcohol and other CNS depressants may increase CNS depressant effects or impairment of psychomotor performance (see section 4.5).

The zuranolone dose should be reduced to 40 mg or permanently discontinued based on the severity of the adverse reaction and the individual sensitivity of the patient to these effects.

A dose reduction of zuranolone should be considered if use with a CNS depressant medicinal product is unavoidable (see section 4.5).

Abuse potential and dependence

Zuranolone has potential for abuse. In a human abuse potential study in recreational CNS depressant users (N=60) zuranolone (30, 60, 90 mg) had dose dependent abuse potential when compared to alprazolam (1.5 mg, 3 mg) on positive subjective measures of “drug liking”, “overall drug liking”, “take drug again”, “high” and “good drug effects”.

Zuranolone may produce physical dependence. In a driving simulation study (N=67), healthy subjects who received 50 mg of zuranolone for up to 7 days (on the 7th day subjects received 50 mg or 100 mg) experienced mild or moderate symptoms of possible withdrawal syndrome.

The risk for developing physical dependence and a subsequent withdrawal syndrome upon abrupt zuranolone discontinuation for individuals who take a higher than recommended dosage and/or use zuranolone for a longer duration than recommended (see section 4.2), has not been evaluated in clinical studies.

In a nonclinical study, convulsions were observed in a dog upon abrupt zuranolone discontinuation following administration daily for 14 days at doses that produced exposures higher than the maximum recommended human dose (see section 5.3).

Caution should be used in individuals with a history of abuse or addiction to alcohol or other substances.

Suicide/suicidal thoughts or clinical worsening:

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs therefore, patients should be closely monitored. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

CNS depressant medicinal products and alcohol

Co-administration of repeated 50 mg daily doses of zuranolone with alcohol or alprazolam led to increased impairment in psychomotor performance. If use with another CNS depressant medicinal products such as opioids, benzodiazepines, nonbenzodiazepine hypnotics, gabapentinoids and sedating antidepressants is unavoidable, dose reduction of zuranolone should be considered (see section 4.4).

Effect of other medicinal products on the pharmacokinetics of zuranolone

CYP3A inducers
Systemic exposure (area under the curve to infinity [AUC_{inf}]) to zuranolone is reduced by 85% in the presence of rifampin (strong CYP3A inducer) (see section 5.2). Concomitant use of zuranolone with a CYP3A inducer decreases the exposure of zuranolone which may reduce the efficacy of zuranolone. Concomitant use of zuranolone with CYP3A inducers should be avoided.

Strong CYP3A inhibitors
Concomitant use of zuranolone with a strong CYP3A inhibitor increases the exposure of zuranolone. Systemic exposure (AUC_{inf}) to zuranolone is increased 62% when administered in combination with itraconazole. The dose of zuranolone should be reduced to 30 mg when used with a strong CYP3A inhibitor (see section 4.2).

Grapefruit juice products are known to inhibit CYP3A and should be avoided.

Non-significant drug interactions

Oral contraceptives
In a clinical study in healthy volunteers, repeated administration of zuranolone did not alter the exposure of simvastatin, a sensitive CYP3A4 substrate, indicating an absence of induction potential with substrates of CYP3A4. Based on *in vitro* studies, zuranolone is not an inhibitor of CYP3A4 at clinically relevant concentrations. Cumulatively these results suggest that zuranolone is unlikely to alter the exposure of oral contraceptives.

Effect of zuranolone on the pharmacokinetics of other medicinal products

Clinical studies

Clinical DDI studies indicate that repeated administration of zuranolone prior to administration of simvastatin (CYP3A substrate) or bupropion (CYP2B6 substrate) did not alter the exposure of simvastatin or bupropion. Zuranolone is not expected to cause a drug interaction through CYP450 enzyme induction.

In vitro studies

Enzyme systems

Zuranolone is not an inhibitor of CYP1A2, CYP2B6, or CYP2C19 and had very low inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4. Zuranolone was a direct inhibitor of CYP2C8 with an IC_{50} of 14 μM. A risk-based analysis that considered factors such as C_{max} and unbound fraction indicated zuranolone is unlikely to cause a clinically significant medicinal product interaction due to inhibition of CYPs.

Efflux and uptake transporters

The interaction of zuranolone with the human BSEP, BCRP, and MDR1 efflux transporters, and human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3,

OCT1, and OCT2 uptake transporters was evaluated. Although zuranolone exhibited mild inhibition of some transporters, further evaluation supports that at clinically relevant concentrations, zuranolone is not expected to inhibit any of the transporters evaluated. Zuranolone is not a substrate of P-glycoprotein.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of zuranolone in pregnant women. Studies in animals have shown reproductive toxicity. Based on findings from animal studies, zuranolone may cause foetal harm (see section 5.3).

Zuranolone is contraindicated during pregnancy and not recommended in women of childbearing potential not using contraception. Patients should use effective contraception during treatment and for 7 days following discontinuation of treatment. Women of childbearing potential should be advised on the use of effective contraception.

Breast-feeding

Data from a clinical lactation study indicate that zuranolone is present in low levels in human breast milk. The calculated maximum relative infant dose (RID) was < 1%. In most subjects, concentrations of zuranolone in breast milk were below the level of quantification limit by 6 days after the last dose (see section 5.2). The effect of zuranolone on breastfed newborns/infants is unknown and there are limited data on the effect on milk production.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for zuranolone and any potential adverse effects on the breastfed child from zuranolone or from the underlying maternal condition.

Fertility

There are no human data on the effects of zuranolone on human fertility. Data from male and female animal studies showed no zuranolone-related effects on fertility or reproduction function at clinically relevant doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Zuranolone has a major influence on the ability to drive and use machines. Two studies evaluated the effects of bedtime zuranolone 30 mg and 50 mg administration on next -morning driving performance, 9 hours after dosing, using a computer-based driving simulation. The driving ability of healthy adults was impaired in a dose-dependent manner following single and repeat nightly administration. A single dose of zuranolone 30 mg or 50 mg caused a statistically significant impairment in next morning- driving performance compared to placebo. The mean effect on driving performance was not statistically significantly different following nightly administration of zuranolone 30 mg compared to placebo on Day 6; however, driving ability was impaired in some subjects taking zuranolone. Statistically significant effects on driving were observed on Day 8 following daily administration of zuranolone 50 mg.

Patients should be counselled not to engage in potentially hazardous activities, such as driving a vehicle or operating machinery, for at least 12 hours after each zuranolone dose. Patients should be advised that they may not be able to assess their own ability to perform these activities (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

Zuranolone was evaluated in two placebo-controlled clinical studies in adults with PND (see section 5.1). Adverse drug reactions (ADRs) with onset up to 3 days after treatment discontinuation are reported at the highest frequency from either study. Serious adverse reaction (SAR) in 1 subject was confusional state.

Treatment discontinuation was reported at 2.0% and dose reductions or interruption was 14.3% in zuranolone-treated subjects. The most reported adverse reaction leading to treatment discontinuation is somnolence (2.0%).

Most ADRs in subjects receiving zuranolone were mild to moderate in intensity. The most frequently reported (≥ 10% in zuranolone 50 mg and greater than placebo) adverse reactions were somnolence, dizziness, and sedation.

Tabulated list of adverse reactions

ADRs are presented in the Table 1. The ADRs are listed by system organ class (SOC) and frequency. Frequency categories were defined according to very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

Table 1. Adverse drug reactions occurring in patients with PND treated with zuranolone

System organ class (SOC)	Adverse drug reaction	Frequency
Psychiatric disorders	Memory impairment	Common
	Confusional state	Common
Nervous system disorders	Somnolence[1]	Very Common
	Dizziness[2]	Very Common
	Sedation	Very Common
	Tremor	Common
Gastrointestinal disorders	Diarrhoea	Common
General disorders and administration site conditions	Fatigue[3]	Common

[1] Include the following preferred terms (PTs): somnolence and hypersomnia.
[2] Include the following PTs: dizziness and vertigo.
[3] Include the following PTs: fatigue and asthenia.

Description of selected adverse reactions

Somnolence and sedation
These ADRs were generally mild to moderate in severity; most appeared within the first two days of treatment, were limited to the on-treatment period, and improved during the treatment course. Most somnolence and sedation ADRs resolved without intervention. In cases where dose reduction due to these ADRs was needed, most subjects completed the treatment course at the reduced dose.

Confusional state
Across the two clinical studies, two subjects experienced confusional state. One subject who received zuranolone 50 mg experienced a non-serious ADR which led to dose reduction to 40 mg. One subject who received zuranolone 30 mg had a SAR at Day 3. The SAR resolved on the same day and treatment was withheld for one day. The subject completed the treatment period on a reduced dose of zuranolone 20 mg without any further symptoms during the study.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

One case of intentional overdose with zuranolone was reported during premarketing clinical trials. The patient took 330 mg (6.5 times the MRHD) of zuranolone and was reported to be in an altered state of consciousness. The event resolved the following morning.

Overdose with zuranolone may result in excessive CNS depressant effects (see section 4.4).

There is no specific antidote for zuranolone overdose. Appropriate supportive measures should be provided as dictated by the patient's clinical status.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants, ATC code: N06AX31

Mechanism of action

Zuranolone is an orally bioavailable, synthetic neuroactive steroid (NAS) with rapid antidepressant effects. Like the endogenous NAS, allopregnanolone, zuranolone exhibits potent positive allosteric modulation of the gamma-aminobutyric acid-A ($GABA_A$) receptor. Zuranolone enhances GABA activity at synaptic and extrasynaptic receptors and has also been shown to increase cell surface expression of $GABA_A$ receptors in *in vitro* studies. Extrasynaptic delta-subunit-containing $GABA_A$ receptors mediate tonic inhibitory currents that play a critical role in controlling network activity in the brain, including synchronisation within and across neural networks. Brain network activity is regulated via a balance of inhibitory (e.g., GABAergic) and excitatory (e.g., glutamatergic) signalling inputs. Abnormalities in brain network activity have been associated with symptoms of depression. Physiological fluctuations in NAS during pregnancy and the peri-partum period are associated with changes in GABAergic signalling, which in susceptible women may result in dysregulated neural network responses and the development of PND. Zuranolone may exert antidepressant effects by enhancing GABAergic inhibition, in particular tonic inhibition, and may provide a mechanism to normalize function in brain networks in regions dysregulated during a major depressive episode (MDE).

Pharmacodynamic effects

Cardiac electrophysiology
At two times the MRHD, zuranolone does not cause clinically significant QTc interval prolongation nor any other clinically significant effect on other electrocardiography (ECG) parameters.

Clinical efficacy and safety

The efficacy of zuranolone for the treatment of women with PND was demonstrated in two randomised, double-blind, parallel-group, placebo controlled, multi□centre studies. In study 217□PPD□301, SKYLARK, zuranolone 50 mg was taken orally once daily. In study 217-PPD-201B, ROBIN, zuranolone 30 mg (another capsule formulation with a higher relative bioavailability) was taken orally once daily. Subjects enrolled in the studies were to have a total score ≥ 26 at baseline in the 17-item Hamilton Depression Rating (HAMD-17) scale. Subjects also met criteria for MDE with peripartum onset as per DSM-5 (Diagnostic and Statistical Manual of

Mental Disorders – 5th edition) criteria. The criteria were limited for both studies to onset of symptoms in the third trimester or within 4 weeks of delivery. Subjects started treatment up to 12 months following childbirth. Subjects were followed for a minimum of 4 weeks after the 14-day treatment course.

Table 2. Population characteristics

Parameter		**217-PPD-301**[†]	**217-PPD-201B**[§]
Age (years) – mean (min, max)		30 (19, 44)	28 (18, 44)
Taking a stable dose of oral antidepressants[*] for at least 30 days before baseline (%)		15	19
Race (%)	White	70	56
	Black or African American	22	41
	Asian	1	1
	Other/Mixed	7	2
Ethnicity (%)	Hispanic or Latino	39	23
Body mass index (kg/m^2) - mean (min, max)		30 (19, 45)	31 (17, 56)
Subjects with PND[**] onset following, and within the first 4 weeks of, childbirth (%)		67	58
HAMD-17 total score at baseline – mean (min, max)		28.7 (21, 36)	28.6 (26, 40)

[*] Antidepressants are identified as medicinal products belonging to ATC level 3 code N06A, medicinal products used to treat depression and related mood disorders.
[**] The term "postnatal depression" is used to represent postpartum depression (i.e., MDE with peripartum onset, or peripartum depression).
[†] Full Analysis Set
[§] Efficacy set

Both studies demonstrated statistical superiority for the primary endpoint, change from baseline at Day 15 in depressive symptoms as measured by the HAMD-17 total score, compared to placebo. There was consistency of treatment effect for the potentially important risk factors of age, body mass index, subjects with PND onset within the first 4 weeks following delivery, and race, with all favouring zuranolone over placebo. Additionally, consistency in the treatment effect was observed by baseline depression severity, as assessed by MADRS (moderate [45.9% and 40.7% of participants in 217-PPD-301 and 217PPD-201B respectively], all others severe), with both the moderate and severe subgroups favouring zuranolone over placebo.

Table 3. Primary endpoint results: change from baseline at Day 15 in the HAMD-17 total score

Study number	**Treatment group**	**N**	**Mean baseline score (SD)**	**LS mean change from baseline (SE)**	**Placebo-adjusted difference (95% CI) p-value**[†§]
217-PPD-301[*]	Zuranolone 50 mg	98	28.6 (2.49)	-15.6 (0.82)	-4.0 (-6.3, -1.7) p = 0.0007
	Placebo	97	28.8 (2.34)	-11.6 (0.82)	
217-PPD-201B[*]	Zuranolone 30 mg[‡]	76	28.4 (2.09)	-17.8 (1.04)	-4.2 (-6.9, -1.5) p = 0.0028
	Placebo	74	28.8 (2.32)	-13.6 (1.07)	

HAMD-17: Hamilton depression rating scale; N: number of subjects in the Full Analysis Set (Study 217-PPD-301) and the Efficacy Set (Study 217-PPD-201B); SD: standard deviation; LS: least squares; SE: standard error; CI: confidence interval. A negative sign indicates clinically meaningful statistically significant improvement on postpartum depressive symptoms.

[*] Results from the 4-item HAM-D subscales (Core, Anxiety, Bech-6, and Maier) supported the results from the HAMD-17 total score for these studies and results from the HAMD-17 individual item scores

showed that the associated symptoms of major depressive episodes were improved with zuranolone treatment, including core symptoms related to mood.

† Among participants with HAMD-17 response at Day 15, three (5.7%) subjects in the 50 mg zuranolone group experienced relapse (defined as at least 2 consecutive HAMD-17 total scores ≥ 20 after Day 15), and none experienced rebound (defined as any HAMD-17 total score greater than or equal to baseline after Day 15).

§ Mixed model for repeated measures (MMRM) was used for the analysis.

‡ Based on exposure estimates in the two studies, the 30 mg formulation administered in 217-PPD-201B is approximately equivalent to 35 mg of zuranolone.

Table 4. Results for secondary endpoints in clinical study 217-PPD-301

Time point	Zuranolone 50 mg (N = 98)		Placebo (N = 97)		Placebo-adjusted difference (95% CI) p-value
	Mean baseline score (SD)	LS mean change from baseline (SE)	Mean baseline score (SD)	LS mean change from baseline (SE)	
Endpoint: change from baseline at Days 3, 28, and 45 in the HAMD-17 total score*†					
Day 3	28.6 (2.49)	-9.5 (0.70)	28.8 (2.34)	-6.1 (0.71)	-3.4 (-5.4, -1.4) p = 0.0008
Day 28		-16.3 (0.88)		-13.4 (0.88)	-2.9 (-5.4, -0.5) p = 0.0203
Day 45§		-17.9 (0.90)		-14.4 (0.90)	-3.5 (-6.0, -1.0) p = 0.0067
Endpoint: change from baseline at Day 15 in the CGI-S score†					
Day 15	5.0 (0.66)	-2.2 (0.14)	4.9 (0.58)	-1.6 (0.14)	-0.6 (-0.9, -0.2) p = 0.0052

CGI-S: Clinical Global Impression Severity scale; HAMD-17: Hamilton depression rating scale; N: number of subjects in the Full Analysis Set; SD: standard deviation; LS: least squares; SE: standard error; CI: confidence interval. Negative sign indicates clinically meaningful statistically significant improvement on postpartum depressive symptoms.

* Median time to first HAMD-17 response was 9 days in the zuranolone 50 mg group compared with 43 days in the placebo group. HAMD-17 response is defined as a 50% or greater reduction from baseline in HAMD-17 total score. Days are calculated from the date of the first dose. Subjects who are not responders are censored at the day of the last available HAMD-17 evaluation.

† Mixed model for repeated measures (MMRM).

§ Observed effect in HAMD-17 total score relative to baseline was also maintained through follow-up to Day 45, p-value < 0.05.

The robustness of the impact of zuranolone on depressive symptoms was supported by the directional consistency of additional endpoints including 9-item Patient Health Questionnaire (PHQ-9) and Edinburgh Postnatal Depression Scale (EPDS) in both studies (217-PPD-301 and 217-PPD-201B) and SF-36 (217-PPD-201B).

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with zuranolone in one or more subsets of the paediatric population in the treatment of postnatal depression (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Once-daily administration of zuranolone 50 mg resulted in accumulation of approximately 1.5-fold in systemic exposures and steady state was achieved in 3 to 5 days.

Following oral administration, peak zuranolone concentrations occur at 5 to 6 hours post-dose.

Effect of food
Following administration of zuranolone 30 mg to healthy volunteers, the maximum serum concentration (C_{max}) increased 228% and the AUC increased 55% with a low-fat meal (400 to 500 calories, 25% fat) compared to fasted conditions. The C_{max} increased 334% and AUC increased 90% with a high-fat meal (800 to 1000 calories, 50% fat) compared to fasted conditions. The time at maximum concentration (t_{max})was not impacted by food. Exposure at doses up to 90 mg remained approximately dose linear with consumption of a moderate-fat meal (700 calories; 30% fat).

Distribution

The volume of distribution of zuranolone following oral administration is high (> 500 L) and was independent of dose. Zuranolone did not distribute preferentially into red blood cells.

Zuranolone is highly protein bound (> 99.5%) to plasma proteins.

Distribution into breast milk
The distribution of zuranolone into human breast milk was studied in a group of 14 healthy lactating women, at least 12 weeks postpartum, treated with daily oral administration of zuranolone 30 mg for 5 days. At steady state (Day 5), the calculated daily infant dose was low (approximately 0.00135 mg/kg/day), reflecting a mean RID of 0.357% (range of 0.067 to 0.832) compared to the maternal dose. From a simulation, the expected mean RID associated with a 50-mg maternal dose was 0.738% for an infant with a milk intake of 150 mL/kg/day and 0.984% for an infant with a milk intake of 200 mL/kg/day.

Lactation did not alter the pharmacokinetic profile, including the fraction unbound in plasma of zuranolone in lactating women relative to other populations.

Biotransformation

Zuranolone undergoes extensive metabolism, with CYP3A identified as a primary enzyme involved. There were no human metabolites circulating at > 10% of total drug-related material and none are considered to contribute to the therapeutic effects of zuranolone.

Elimination

The terminal half-life ($t_{1/2}$) of zuranolone is approximately 19.7 to 24.6 hours in an adult population. The clearance of zuranolone was independent of dose. The mean apparent clearance (CL/F) of zuranolone is 32.7 L/h.

Excretion

Following oral administration of radiolabelled zuranolone, 45% of the dose was recovered in urine as metabolites with negligible unchanged zuranolone and 41% in faeces as metabolites with less than 2% as unchanged zuranolone.

Pharmacokinetics in special patient groups

Weight, race, or age
The pharmacokinetics (PK) of zuranolone was similar between healthy subjects and subjects with PND.

Black or African American subjects had a 14% higher CL/F compared to subjects of other races (Asian, White, or other) but this increase was not clinically meaningful.

No dose adjustments are necessary based on weight, race, or age.

Renal impairment
Exposure to zuranolone was increased in patients with moderate (eGFR 30 to 59 mL/min) and severe (eGFR 15 to 29 mL/min) renal impairment (see section 4.2). Zuranolone has not been studied in patients with eGFR of < 15 mL/min or patients requiring dialysis (see section 4.2).

Hepatic impairment
C_{max} and AUC_{inf} for zuranolone were unchanged in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment compared to matched healthy subjects. C_{max} was 24% lower and AUC_{inf} was 56% higher in patients with severe (Child-Pugh class C) hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Reproductive toxicity

In the pivotal rat embryo-foetal development study, a low incidence of foetal malformations was noted at all dose levels investigated in the study (2.5, 7.5, and 22.5 mg/kg/day) which were considered treatment-related at 22.5 mg/kg/day. The developmental no observed adverse effect level (NOAEL) was 7.5 mg/kg/day. Exposures at this dose are approximately 6.9- to 7.7-fold above the expected exposures in humans.

Oral administration of zuranolone (0, 30, 100, or 300 mg/kg/day) to pregnant mice during organogenesis resulted in maternal dose-dependent sedation which was severe at 300 mg/kg/day. Adverse reduced foetal body weight occurred at 300 mg/kg/day, which was associated with incomplete or no skeletal ossification. There was an increased incidence of cleft palate at 300 mg/kg/day (6.6 times the AUC exposure at the MRHD). The NOAEL for embryofoetal development was 100 mg/kg/day with maternal exposures (AUC) approximately 4.5 times that in humans at the MRHD.

In a pre□/postnatal development study in rats, oral administration of zuranolone during pregnancy and lactation at doses of 0, 1, 4, or 10 mg/kg/day resulted in maternal mortality and adverse clinical signs at 4 and 10 mg/kg/day, corresponding to exposures approximately 6-fold and 8-fold higher, respectively, than the MRHD. An increase in postnatal pup mortality occurred at ≥ 4 mg/kg/day. Decrease in body weight gain occurred at 4 mg/kg/day in males and females during the preweaning period, and in males during the postweaning period. There were no treatment-related effects on sexual maturation, neurobehavioural assessments, or reproductive capability in offspring at up to 4 mg/kg/day. There was no pre- or postnatal developmental toxicity at 1 mg/kg/day, corresponding to 2-fold the MRHD.

At zuranolone exposures 5.6-fold greater than MRHD, a relative elevation in neuronal death was observed in rats exposed to a single dose of zuranolone on postnatal Day 7, which corresponds in humans to a period of brain development beginning during the third trimester of pregnancy and continuing up to a few years after birth. No neuronal death was observed at exposures similar to MRHD.

Abuse potential and dependence

In an episodic dosing toxicology study in dogs (14 days of dosing followed by either 21 or 42 days without dosing in between 14-day dosing regimens; 6 cycles), one male was observed to have a convulsion 3 days after the end of the first 14-day dosing cycle. The exposure reached at this dose level was greater than that produced at the maximum recommended human dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Colloidal silicon dioxide (E551)
Croscarmellose sodium (E468)
Mannitol (E421)
Microcrystalline cellulose (E460)
Silica, colloidal anhydrous (E551)
Sodium stearyl fumarate

Capsule shell

Gelatin (E441)
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

Capsule print (black ink)

Ammonium hydroxide (E527)
Black iron oxide (E172)
Propylene glycol (E1520)
Shellac glaze (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years (PVC laminated PCTFE aluminium blister)
5 years (HDPE bottles)

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child resistant, foil induction-sealed polypropylene closures. Pack sizes of 14 or 28 hard capsules.

Polyvinyl chloride (PVC) laminated polychlorotrifluoroethylene (PCTFE) aluminium blister. Pack size of 28 capsules in 1 carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 22407/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/08/2025

10 DATE OF REVISION OF THE TEXT

21/04/2026