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EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR ZURZUVAE (ZURANOLONE)

RMP version number:	1.0
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QPPV name: Jana Hyankova, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

Not applicable - no other versions of zuranolone EU RMP are currently under evaluation.

Details of currently approved RMP

Not applicable for initial marketing authorisation application submission.

Rationale for submitting an updated RMP

Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP

Not applicable for initial marketing authorisation application submission.

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PART VII - ANNEXES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
ADT	antidepressant therapy
AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMI	Body Mass Index
CDP	clinical development programme
CLP	clinical pharmacology
CNS	central nervous system
CSR	clinical study report
DCO	Data Cut-Off
DCT	Data collection tool
EPDS	Edinburgh Postnatal Depression Scale
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid-gated chloride channel
ICH	International Conference on Harmonisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
MoA	mechanism of action
MDD	major depressive disorder
MDE	major depressive episode
N	number of participants with events
NAS	neuroactive steroid
NOAEL	no observed adverse effect level
PAM	positive allosteric modulator
PASS	Post-Authorisation Safety Study(ies)
PC	placebo-controlled
PL	package leaflet
PWC-20	20 item Physician Withdrawal Checklist
PPD	postpartum depression
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RoW	rest of world

Abbreviation	Definition
SmPC	Summary of Product Characteristics (EU)
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Zuranolone
Pharmacotherapeutic group(s) (ATC Code)	N06AX31
Marketing Authorisation Applicant	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Zurzuvae
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Zuranolone is a synthetic neuroactive steroid (NAS) that exhibits potent positive allosteric modulation of gamma-aminobutyric acid-A ($GABA_A$) receptor.
	Summary of mode of action: Zuranolone enhances GABAergic activity at synaptic and extrasynaptic $GABA_A$ receptors and has also been shown to increase cell surface expression of $GABA_A$ receptors in *in-vitro* studies. Zuranolone may exert antidepressant effects by enhancing GABAergic inhibition.
	Important information about its composition: Zuranolone is a white to off-white, non-hygroscopic, crystalline solid. It is slightly soluble to soluble in the organic solvents used in the manufacturing process and practically insoluble in water.
Hyperlink to the Product Information	See eCTD Module 1.3.1.
Indication(s) in the EEA	**Current:** Zurzuvae is indicated for the treatment of postpartum depression (PPD) in adults following childbirth.
Dosage in the EEA	**Current:** The recommended dose of zuranolone is 50◦mg (two 25◦mg capsules) taken orally once daily for 14 days as a single course of treatment. Zuranolone may be used alone or with stable background oral antidepressant therapy.

Pharmaceutical form(s) and strengths	**Current *(if applicable)*:** *Form:* Hard capsules *Strength:* 20 mg, 25mg, and 30 mg
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

SI.1 Epidemiology of Postpartum Depression

Epidemiology data for the proposed patient population (PPD) is provided in the sections below.

PPD is a serious psychiatric condition that is temporally and pathophysiologically related to pregnancy. PPD is identified as one of the most common complications of pregnancy and childbirth to occur in the puerperium [Howard 2014] and can have devastating consequences for the woman, the newborn infant, and her family [Fihrer 2009; Moore Simas 2019; Verbeek 2012].

PPD is the occurrence of an MDE with peripartum onset (during pregnancy or up to 4 weeks after delivery), with MDE defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision [American Psychiatric Association 2022] as characterized by the presence of 5 or more of the following symptoms: Depressed mood, diminished interest or pleasure, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, diminished ability to concentrate, and recurrent thoughts of death, suicidal ideation or attempt, that have been present during the same 2-week period and represent a change from previous functioning; with at least 1 of the symptoms being either depressed mood or loss of interest or pleasure.

While the DSM-5-Text Revision defines PPD as an MDE occurring with a peripartum onset during pregnancy or in the 4 weeks following delivery, many disease occurrence studies assess the development of PPD using longer timeframes of up to 12 months after delivery.

Participants in the zuranolone clinical studies comprised a diverse population of women with PPD across the child-bearing age range, albeit recruited predominantly in the US. The clinical study results are applicable to the UK and European populations based on underlying pathophysiology and analyses across several variables. The PK, safety, and efficacy of zuranolone are generally insensitive to intrinsic and extrinsic factors, with consistency of treatment effect in Studies 217-PPD-301 and 217-PPD-201B in subgroup analyses favouring zuranolone over placebo based on potential risk factors including age, BMI, onset time point of PPD, family history of PPD, baseline anxiety, race, education, and hormonal contraceptive use. Notably, the physiologic and hormonal changes related to pregnancy and parturition are independent of ethnic background and are shared across geographies [Stewart and Vigod 2016; NICE 2020], as reflected in the consistency in the prevalence of PPD symptoms across the US (approximately 13% [Bauman 2020]), Europe (approximately 12% as described herein), and the UK (approximately 10% [Matijasevich 2009; NHS 2022]). Prevalence of relevant comorbidities and comedication usage is also largely similar among the PPD patient populations across the US, UK, and EU; for example, comorbid anxiety [Falah-Hassani 2017], comorbid sleep disturbances [Yang 2020] and use of various over-the-counter and prescription medications during pregnancy [Lupattelli 2014] are found in similar ranges across US and European regions.

Incidence

As PPD risk exists only in the specific peripartum period, studies of incidence require detailed methods to identify risk windows and exclude women with previously existing relevant symptoms or diagnoses. Given the challenges in incidence estimation, studies of PPD occurrence more accurately report prevalence, rather than incidence. Accordingly, PPD disease occurrence information is presented solely in the prevalence section.

Prevalence

Median estimates of PPD symptom prevalence, which studies largely measure using symptom scales, are as follows.

The global prevalence is estimated to be 14.5%, with range 4.3% to 31.8% [Ahmed 2021; Alam 2021; Alasoom and Koura 2014; Alhusaini 2022; Alonazi and Jahan 2022; Bauman 2020; Bauman 2020b; Cena 2021; Chalise 2020; Choi 2021; Clavenna 2017; Dekel 2019; Della Corte 2022; Dikmen-Yildiz 2017; Gan 2019; Gheorghe 2021; Hanach 2023; Inthaphatha 2020; Jaeschke 2017; Kikuchi 2021; Lara 2015; Liu 2020; Matsumura 2019; Matsuoka 2021; Melo 2012; Pataky and Ehlert 2020; Peng 2021; Roumieh 2019; Roysted-Solas 2022; Shao 2021; Shi 2021; Wu 2022; Xayyabouapha 2022].

In Europe, the estimated prevalence of PPD symptoms is 12.4% of women with a recent live birth [Dekel 2019], which is the median estimate from European studies with findings ranging from 4.7% [Clavenna 2017] to 19.9% [Cena 2021; Jaeschke 2017; Clavenna 2017; Dekel 2019;Pataky and Ehlert 2020; Della Corte 2022; Holm 2022]. Among women screening positive for PPD symptoms on screening instruments like the Edinburgh Postnatal Depression Scale, it is estimated that 21% meet DSM criteria for a diagnosis of PPD [Levis 2020]. In the UK, a cohort study based upon UK health records of women who had given live birth between 2000 and 2013 reported 11% of women with at least 1 record indicating depression, postnatal depression, or symptoms of depression in the year after delivery [Petersen 2018]. In the population-based National Survey of Women's Experience of Maternity Care conducted in the UK in 2014, 9.3% of women with a recent birth screened positive for PPD symptoms [Fellmeth 2019].

The estimated prevalence of PPD symptoms is 14.6% for Asia [Alam 2021; Chalise 2020; Choi 2021; Gan 2019; Inthaphatha 2020; Kikuchi 2021; Liu 2020; Matsumura 2019; Matsuoka 2021; Peng 2021; Roysted-Solas 2022; Shao 2021; Shi 2021; Wu 2022; Xayyabouapha 2022], 12.3% for Latin America [Lara 2015; Melo 2012], 14.4% for North America [Bauman 2020; Gheorghe 2021], and 16.2% for the Middle East and North Africa [Ahmed 2021; Alasoom and Koura 2014; Alhusaini 2022; Alonazi and Jahan 2022; Dikmen-Yildiz 2017; Hanach 2023; Roumieh 2019].

- **Demographics of the Population in the Proposed Indication and Risk Factors for the Disease**

Age, Sex, and Ethnic Origin

PPD occurs in women of childbearing age across ethnicities and socio-economic status [NICE 2020; World Health Organization 2024]. Biologically, reproductive potential is highest in the late teenage years through the 20s and begins to decline after the age of 30 [American College of Obstetricians and Gynecologists 2024]. A medical record study of women giving birth in the UK

found that postpartum women under the age of 30 were more likely to have a diagnosis of PPD [Petersen 2018].

Risk Factors for the Disease

There are a variety of risk factors for PPD, and, like other psychiatric disorders, there does not appear to be 1 specific cause. The depression diagnosis manifests from a complex combination of biological, psychosocial, environmental, and possibly genetic factors [Couto 2015; Guintivano 2023]. Strong predictors of PPD include a history of depression or anxiety disorder [Beck 2001; Bloch 2006; Howell 2006; Martini 2015; O'Hara 2009; Roberson 2016; Silverman 2020; Silverman 2017; Vivilaki 2021]. The physical health of the mother is also important with conditions such as anaemia, obesity, diabetes, and preeclampsia noted as risk factors [Arora and Aeri 2021; Koutra 2018; Miller 2016; Molyneaux 2014; Ruohomaki 2018; Steinig 2017; Tuthill 2021; Wassef 2019; Ye 2021]. A woman's experience in childbirth, such as a traumatic experience, can contribute to the development of depressive symptoms [Bay and Sayiner 2021]. Lastly, stressful life events and inadequate social support are risk factors for PPD [Bauman 2020; Kızılırmak 2020; Mukherjee 2017; Razurel 2017]. A medical record study of women giving birth in the UK found that women experiencing social deprivation were more likely to be diagnosed with PPD compared to women not experiencing social deprivation [Petersen 2018].

Main existing treatment options

Current treatment options for PPD include both psychotherapeutic and limited pharmacological approaches.

Psychotherapeutic approaches include in-home midwife care, group therapy, interpersonal therapy, cognitive behavioural therapy, psychoeducation, and psychodynamic therapy [Branquinho 2021].

Although ADTs have not received regulatory approval for the specific indication of PPD, first line treatment recommendations comprise cautious use of oral ADTs for moderate-to-severe PPD [Kittel-Schneider 2022; NICE 2020]. This approach is based primarily on research among patients with MDD, rather than extensive studies in PPD [Austin 2013], and high-quality data to support the efficacy of MDD-approved ADTs in PPD are limited [Brown 2021]. The most frequently recommended ADTs include selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, and tricyclic ADTs, with paroxetine and sertraline preferred if the mother is breastfeeding. Most pharmacologic classes of ADTs used to treat PPD act through monoaminergic mechanisms (e.g., selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors). These agents may take up to 4 - 6 weeks for the onset of antidepressant effects and evidence suggests that this may be even more prolonged in PPD than in MDD [Hendrick 2000]. Common and persistent side effects associated with approved antidepressants include gastrointestinal symptoms, sleep disturbances, weight gain, and sexual dysfunction [Clayton 2002; Fava 2000; Papakostas 2008]. More serious effects such as serotonin syndrome are also a risk. Treatment nonadherence rates are high with ADTs; combined with perceived stigma around treatment and potential for concerns around the impact on breastfeeding, these therapies with their relatively slow onset of symptomatic relief have not been optimal for PPD [Clayton 2002; Fava 2000; Goodman 2009; Papakostas 2008; Sansone and Sansone 2012].

In the US, zuranolone was approved for the treatment of PPD in adults in Aug 2023 [U.S. Food & Drug Administration 2023a]. Additionally, another drug, brexanolone, received approval in 2019 [U.S. Food & Drug Administration 2019]. Brexanolone requires inpatient treatment with continuous intravenous infusion over the course of 60 hours [U.S. Food & Drug Administration 2022]. In contrast, zuranolone is an oral medication taken for 14 days [U.S. Food & Drug Administration 2023b]. Brexanolone and zuranolone both provide benefits over conventional antidepressants as they provide more rapid symptom relief which is critical to both the health and safety of the mother and child; however, they are currently only commercially available in the US.

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

The duration of PPD may vary depending on several factors, including sociodemographic factors, symptom severity, history of mood disorders, presence of gestational diabetes mellitus, and having prior live births [Putnick 2020]. Studies conducted in community settings have found that among women who meet PPD criteria within the first 3 months of giving birth, 30% - 62% (median 35.5%) still meet PPD criteria at 6 months [Vliegen 2014]. In clinical settings, studies have found approximately 50% of PPD patients have persistence of depressive symptoms throughout and beyond the first postnatal year [Vliegen 2014]. Women with postpartum depressive symptoms are at higher likelihood of recurrence in subsequent pregnancies [Letourneau 2012].

Maternal PPD has negative consequences for mothers and infants. The potential impact on the mother's psychological health, quality of life, and interactions with their infant and partner may result in downstream consequences for the baby that can continue into childhood. Infants of depressed mothers are more likely to suffer from poor health, such as failure to thrive, and sleep-related problems due to long-lasting disturbances of mother-child interactions and risky parenting practices induced by PPD [Field 2010]. Long-term exposure to a mother with PPD during infancy has also been reported to impair children's cognitive development, social-emotional development (avoidant attachment, adjustment problems, and internalising problems), and behavioural development (i.e., antisocial, aggressive, and hyperactive problems) [Letourneau 2012].

One of the most severe consequences of PPD is maternal mortality, with death by suicide being a leading cause of mortality in the postpartum period, accounting for approximately 20% of postpartum deaths. Women with a psychiatric diagnosis are at a higher risk for suicide in the perinatal period, and depression is one of the most common diagnoses among perinatal patients who report suicidal ideation or attempt or complete suicide [Chin 2022].

Important Co-Morbidities Found in the Target Population

Anxiety

Comorbid anxiety is common among women with PPD [Della Corte 2022; Falah-Hassani 2017; Wisner 2013] and is associated with high symptom severity, suicidality, chronicity, and treatment resistance in the mother and cognitive, behavioural, and emotional development challenges for the baby [Falah-Hassani 2017].

Anxiety in the prenatal period among women with PPD was reported in 59.5% of women in a study in Italy [Della Corte 2022].

Data from England's 2020 National Maternity Survey indicated that at 3 months postpartum, 14% self-reported postnatal anxiety assessed by the EPDS anxiety sub-scale (EPDS-3A), and among those with anxiety, 53% reported comorbid PPD based on having sought help from a health care professional [Fellmeth 2022].

Among 10,000 women in the US who screened positive for postpartum depressive symptoms, 82.9% also screened positive for comorbid anxiety, indicating that the co-occurrence of PPD and anxiety disorders is common [Wisner 2013].

Substance Use and Abuse

In a US study that contacted women 9 - 10 months after giving birth, 26% of the women reported substance use (defined as opioid misuse, excessive alcohol use, or any use of tobacco, marijuana or other substances) since giving birth [Stewart 2023]. By depression status, substance use was reported by 48.5% of the postpartum women with depressive symptoms in the past 30 days, compared to 24.0% of those without depressive symptoms in the past 30 days [Stewart 2023]. Substance use during pregnancy is associated with a higher risk of PPD across numerous studies [Pacho 2023].

Bipolar Disorder

Childbirth can potentially trigger onset of bipolar disorder or a recurrence of hypomania, mania, or bipolar depression in the postpartum period. The highest risk period in a woman's life for switching from MDD to bipolar disorder is following childbirth [Sharma 2018]. A reported 20% to 35% of women with postpartum depressive symptoms met the criteria for bipolar disorder [Sharma 2017]. Distinguishing between bipolar depression and unipolar depression in postpartum women is crucial as antidepressant monotherapy has the potential to increase rapid cycling and the risk for mania, hypomania, or treatment resistance in individuals with bipolar disorder [Sharma and Khan 2010].

Sleep Disturbances

Poor sleep quality is common in the postpartum period. A meta-analysis of observational studies examining the prevalence of poor sleep quality in perinatal and postnatal women found that postnatal women reported a higher prevalence of poor-quality sleep than perinatal women (67.2% and 44.5%, respectively, $P < 0.001$). Studies conducted in North America reported the highest prevalence of poor sleep quality (74.7%), followed by Asia (53.6%) and Europe (50.4%) [Yang 2020].

PPD symptoms and poor sleep quality are positively associated [Dorheim 2009; Okun 2018]. In a study from Norway, women with PPD symptoms were significantly more likely to report poor sleep quality, compared to those without PPD symptoms (89% vs. 51%, adjusted odds ratio 7.4, 95% CI: 4.6 - 8.9) [Dorheim 2009]. A study conducted in a large teaching hospital in the northeast of England found that scores on the EPDS and General Sleep Disturbances Scale were consistently correlated at 6 weeks and 12 weeks postpartum [Rudzik 2023].

Insomnia was the most common sleep disorder diagnosis among postpartum women up to 12 months after delivery in the US (affecting 68% of postpartum women with a sleep disorder diagnosis) [Sultan 2023].

Anaemia

According to the World Health Organization, anaemia is a serious global public health problem particularly affecting pregnant and postpartum women, with an estimated prevalence of 37% among pregnant women, and 30% among women 15 - 49 years of age [Organization 2023].

In the UK, the prevalence of anaemia was found to be 24% in a multicentre national study [Barroso 2011] and a two-centre English study found 46% of women had anaemia at the first prenatal visit or at the 28-week check [Nair 2017].

A significant association between postpartum anaemia and PPD has been reported in several studies [Albacar 2011; Eckerdal 2016; Xu 2018; Wassef 2019; Azami 2019; Kang 2020]. Studies in Europe have found that 39% of women with PPD had depleted iron stores [Albacar 2011] and that 50% of women with PPD at 6 weeks postpartum were anaemic at the time of delivery [Eckerdal 2016].

Concomitant medications

The most common medications used in the postpartum period have been reported to be analgesics/antipyretics, antibacterials/antibiotics, iron preparations, and oral contraceptives [Saha 2015].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies with potential relevance to human usage are described in Table 2.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Toxicity Studies	
Key issues identified from acute or repeat-dose toxicity studies: • Sedation was the primary observation in non-clinical species. Dose-dependent increases in the depth of sedation with related observations including but not limited to decreased activity/locomotor activity, ataxia, loss of righting reflex, recumbency, ptosis, coolness to touch (hypothermia), altered respiration. Sedation and sequelae were observed in all species evaluated and is an expected pharmacology based on the MoA. • Convulsions were noted in the dog 3--month, 9-month, and periodic dosing studies. The convulsions were noted during morning evaluations prior to dosing when zuranolone plasma concentrations would be at the lowest/trough levels or following cessation of dosing. This may also be consistent with an acute withdrawal-type response following prolonged administration at high dose levels to dogs, a species sensitive to different abstinence syndromes [Authier 2016; Bassett 2014]. Dogs were found dead or euthanized *in extremis* in the 3-month study, in the 9-month study, and in the periodic dosing study. Animal loss in dogs was considered consistent with withdrawal type effects which have been observed following termination of chronic dosing of GABA-modulating compounds in dogs [McNicholas 1983; Löscher 1989].	Sedation is consistent with the pharmacology of zuranolone. Sedation and decreased activity are a risk for humans and are related to known AEs in the clinic. Therefore, sedation is considered an adverse response to zuranolone that is anticipated in humans. Based on the pharmacology of zuranolone, and the dose-related sedation findings, it would be anticipated that an overdose of zuranolone in humans may be accompanied by serious CNS depression manifestations. Dogs are a species known to exhibit withdrawal-type responses following GABA modulators. Convulsions observed during dosing periods in the 3-month and 9-month studies were consistent with a withdrawal-type response. Withdrawal effects are considered a potential risk for zuranolone. No seizures consistent with withdrawal events have been reported with zuranolone in clinical trials.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Reproductive/Developmental Toxicity	
There were no zuranolone-related effects on fertility. Malformations were noted in the rat embryo-foetal development study at a margin of 15.3× MRHD. The NOAEL for developmental toxicity in rats was 7.7× MRHD. 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 embryofetal development was 100 mg/kg/day with maternal exposures (AUC) approximately 4.5 times that in humans at the MRHD. There were no zuranolone-related findings in the rabbit embryo-foetal development study. However, based on high exposure variability and lack of exposure dose response, the study was considered inadequate for assessment of developmental toxicity assessment. In the rat pre and postnatal development study the NOAEL margin was 2× based on lactational phase loss of pups and body weight effects in male pups of the F1 generation. A single dose administration to postnatal day 7 rats indicated elevated neurodegeneration at a margin 5.6× MRHD. The NOAEL was 1.4× MRHD. Results included increased apoptotic neurodegeneration relative to controls in 1 area of the brain (subiculum) in both males and females. The region affected was small and variations in staining were noted between levels of the subiculum. A juvenile toxicology study dosed from postnatal days 22 - 71 demonstrated sedation and pup loss	Zuranolone was not found to have adverse effects on either male or female fertility and no impact on human fertility is anticipated. The NOAEL in the rat embryofetal development study is approximately 6.9 to 7.7-fold above the expected exposures in humans. Interpretation of the postnatal day 7 single dose study is challenging due to the inherent plasticity of the developing brain during this period in rats and humans. Zuranolone shows similar clinical observations in juveniles as in adult rats. The study suggests risks for increased motor activity and delayed female maturation at exposures greater than MRHD. In rats postnatal day 22 - 71 represents weaning to adulthood, which in humans would approximate about 18 months to 2 years through adulthood per Appendix A, Table A1 of ICH S11. Consequently, the risk of embryofetal toxicity is considered as a potential risk. The use of zuranolone is contraindicated during pregnancy and therefore exposure of women to zuranolone during pregnancy is not anticipated.

SAFETY FINDING	RELEVANCE TO HUMAN USE
at higher doses. There were no zuranolone-related effects on male sexual maturation, ophthalmology, acoustic startle response and habituation, learning and memory, reproductive function, bone length or density, or clinical or anatomic pathology parameters in either sex at any dose level. However, there was delayed female sexual maturation at the highest and intermediate doses evaluated. Additionally, increased motor activity in the high dose males and high and intermediate dose females. The NOAELs in this study were 3.1× and 2.1× MRHD for males and females, respectively.	
Genotoxicity	
Zuranolone was not mutagenic or clastogenic in a standard battery of ICH recommended genotoxicity assays.	No evidence of genotoxicity has been observed in non-clinical studies, therefore, no adverse effects in humans are anticipated.
Carcinogenicity	
Zuranolone did not demonstrate carcinogenic potential in a 26-week transgenic mouse carcinogenicity study or in a 104-week rat carcinogenicity study.	No evidence of carcinogenicity has been observed in non-clinical studies, therefore, no adverse effects in humans are anticipated.
Safety Pharmacology	
Central Nervous System: In the rat neurobehavioral assessment, zuranolone produced expected sedation and decreases in activity and locomotion. These effects were seen at 3× MRHD. **Cardiovascular System** The concentration resulting in 20% inhibition for human ether-à-go-go-related gene inhibition by zuranolone was 2.4 µM, approximately 2080× MRHD. There were no zuranolone-related effects on cardiovascular parameters, including QTc, in the telemeterised dog study assessed to 7.1× MRHD. **Respiratory System** There were no zuranolone-related effects on respiratory parameters in male rats to 3.0× MRHD.	There is an adequate safety margin to the relevant zuranolone dose in humans. No cardiovascular or respiratory zuranolone-related effects in humans are anticipated.
Other Toxicity-Related Information	

SAFETY FINDING	RELEVANCE TO HUMAN USE
Zuranolone demonstrated dose-responsive generalization to midazolam in rats; however, the highest dose evaluated had decreased responses due to sedation. Zuranolone did not support cocaine reinforcement in rats indicating that there was not a signal for self-administration. Zuranolone was associated with mild withdrawal in female rats (body weight loss) with a NOEL of 3.4× MRHD.	Non-clinical abuse potential studies suggest a low risk for human abuse.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The evaluations of safety presented in this EU RMP (in support of the overall benefit-risk assessment of zuranolone) focuses primarily upon the review of integrated data from the following Phase 3 studies, conducted in participants with PPD.

Study 217 PPD-201B and Study 217 PPD-301, both randomised, double-blind, PC studies of participants with PPD, which consisted of a 14-day double-blind treatment period and a follow-up period through Day 45.

As of 03 Feb 2024, data from 347 patients were included in the pooled safety dataset, and 176 participants were dosed with either 30 mg or 50 mg zuranolone. Exposure data, stratified by age, dose, ethnic origin/race are presented in Table 3, Table 4, Table 5, Table 6, and Table 7.

Table 3: Duration of Exposure

	Placebo (N = 171)	**30 mg Zuranolone (N = 78)**	**50 mg Zuranolone (N = 98)**	**All Zuranolone (N = 176)**
Duration of Exposure (days) [1]				
Mean	13.6	13.8	13.3	13.5
SD	2.00	1.97	2.19	2.10
Median	14.0	14.0	14.0	14.0
Min, Max	2, 15	2, 17	3, 15	2, 17

IP = Investigational Product.
Note: Treatment group percentages are based on the number of participants who received any IP (i.e., n/N).
[1] For studies with daily dosing, duration of exposure is defined as date of last dose - date of first dose + 1, including days when the dose was missed.
Source: 5.3.5.3, Pooled Safety Table 18

Table 4: Duration of Exposure Group

	Placebo (N = 171)	**30 mg Zuranolone (N = 78)**	**50 mg Zuranolone (N = 98)**	**All Zuranolone (N = 176)**
Duration of Exposure (days) [1]				
Mean	13.6	13.8	13.3	13.5
< 14	**13 (7.6)**	**3 (3.8)**	**14 (14.3)**	**17 (9.7)**
1 - 3	4 (2.3)	2 (2.6)	1 (1.0)	3 (1.7)
4 - 7	2 (1.2)	0	6 (6.1)	6 (3.4)
8 - 13	7 (4.1)	1 (1.3)	7 (7.1)	8 (4.5)
≥ 14	**158 (92.4)**	**75 (96.2)**	**84 (85.7)**	**159 (90.3)**
14	153 (89.5)	70 (89.7)	83 (84.7)	153 (86.9)
> 14	5 (2.9)	5 (6.4)	1 (1.0)	6 (3.4)
Person-Time (weeks)	331.9	153.4	186.1	339.6

IP = Investigational Product.
Note: Treatment group percentages are based on the number of participants who received any IP (i.e., n/N).
[1] For studies with daily dosing, duration of exposure is defined as date of last dose - date of first dose + 1, including days when the dose was missed.
Source: 5.3.5.3, Pooled Safety Table 18

Table 5: Cumulative Exposure to Study Drug by Age Group

Age Group (years)	**Number of Participants Exposed to Placebo (N = 171) n (%)**	**Person-Time (Weeks)**	**Number of Participants Exposed to Zuranolone (N = 176) n (%)**	**Person-Time (Weeks)**
N	171	331.9	176	339.6
18 - 24	37 (21.6)	74.1	36 (20.5)	72.4
25 - 45	134 (78.4)	257.7	140 (79.5)	267.1

Note: Age is calculated at the first dose of study drug. No participants over 45 years were enrolled in PPD PC Pool.
Source: 5.3.5.3, Pooled Safety Table 21

Table 6: Exposure to Study Drug by Dose

Dose of Exposure	Number of Participants (N = 347) n (%)	Person-Time (Weeks)
Placebo	171 (49.3)	331.9
Zuranolone	176 (50.7)	339.6
30 mg	78 (22.5)	153.4
50 mg	98 (28.2)	186.1

Note: In cases where a participant's dose was reduced (e.g., from 50 mg to 40 mg for safety concerns or lack of tolerability), participants will be categorized according to the highest dose of zuranolone received during the treatment period.
Source: 5.3.5.3, Pooled Safety Table 23

Table 7: Exposure to Study Drug by Race

			Number of Participants with Zuranolone Exposure					
Race	Placebo (N=171) n (%)	Person-Time (Weeks)	30 mg (N=78) n (%)	Person-Time (Weeks)	50 mg (N=98) n (%)	Person-Time (Weeks)	All Zuranolone (N=176) n (%)	Person-Time (Weeks)
White	108 (63.2)	215.3	45 (57.7)	87	68 (69.4)	130	113 (64.2)	217
Black or African American	50 (29.2)	91.6	31 (39.7)	62.4	25 (25.5)	46.7	56 (31.8)	109.1
Asian	2 (1.2)	4	1 (1.3)	2	1 (1.0)	2	2 (1.1)	4
Other/ Mixed	10 (5.8)	19	1 (1.3)	2	3 (3.1)	6	4 (2.3)	8
Not Reported	1 (0.6)	2	0	0	1 (1.0)	1.4	1 (0.6)	1.4

Note: In cases where a participant's dose was reduced (e.g., from 50 mg to 40 mg for safety concerns or lack of tolerability), participants will be categorized according to the highest dose of zuranolone received during the treatment period.
Source: 5.3.5.3, Pooled Safety Table 25

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

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The zuranolone clinical development programme has employed specific exclusion criteria which were either related to the evaluation of efficacy (to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), or were related to safety (in order to protect trial patients from potential risks associated with investigational product administration), or were Good Clinical Practice related (e.g., to ensure that proper follow-up was possible).

A review of the key exclusion criteria in pivotal studies, and an assessment of their relevance to be considered as areas of missing information are presented in Table 8.

Table 8: Discussion of exclusion criteria in relation to the assessment of missing information

Criteria	Reason for Being an Exclusion Criterion	Is it Considered Missing Information?	Rationale
Current significant risk of suicide or attempted suicide associated with the current episode of PPD.	To avoid confounding the evaluation of safety outcomes	No	There is no evidence to suggest that the use of zuranolone in patients leads to a specific safety concern of suicide attempt, or a different outcome to previously identified risks.
Recent history or active clinically significant disease, and/or any other acute or chronic condition that would limit the ability to participate or complete the study. BMI ≤ 18 or ≥ 45 kg/m^2 at screening. Cancer diagnosis or treatment within the previous year to screening. Or any plans to undergo elective surgery during the study.	To avoid confounding the evaluation of safety outcomes	No	The exclusion was not due to a specific safety concern with zuranolone. There is no evidence to suggest that the use of zuranolone in patients with a significant disease or BMI leads to a specific safety concern, or a different outcome to previously identified risks.
Allergy to zuranolone, allopregnanolone, or related compounds.	Standard precautionary measure to avoid hypersensitivity reaction to this product.	No	Zuranolone should not be used in patients with hypersensitivity to any component of the product.

Criteria	Reason for Being an Exclusion Criterion	Is it Considered Missing Information?	Rationale
Participant has active psychosis.	To avoid confounding the evaluation of safety outcomes and/or efficacy	No	The exclusion was not due to a specific safety concern with zuranolone. There is no evidence to suggest that the use of zuranolone in these patients leads to a specific safety concern, or a different outcome to previously identified risks, when zuranolone is used according to the product label.
Medical history of: • Seizures, bipolar disorder, schizophrenia and/or schizoaffective disorder and/or nonfebrile seizures. • Vagus nerve stimulation, electroconvulsive therapy, or patient has taken ketamine within the current major depressive episode.	To avoid confounding the evaluation of efficacy.	No	The exclusion was not due to a specific safety concern with zuranolone. There is no evidence to suggest that the use of zuranolone in these patients leads to a specific safety concern, or a different outcome to previously identified risks, when zuranolone is used according to the product label.
Medical history of: • Sleep apnoea. • Clinically significant abnormal 12-lead ECG at the Screening or on Day 1 of any treatment period.	To avoid confounding the evaluation of safety outcomes and/or efficacy	No	The exclusion was not due to a specific safety concern with zuranolone. There is no evidence to suggest that the use of zuranolone in these patients leads to a specific safety concern, or a different outcome to previously identified risks, when zuranolone is used according to the product label.
Participant's history of active alcoholism or substance use disorder (including benzodiazepines) in the 12 months prior to screening.	To avoid confounding the evaluation of safety outcomes	No	This exclusion was a safety precaution. Alcohol and other CNS depressants may increase impairment of psychomotor performance or CNS depressant effects. Therefore, participants with a condition predisposing them to take alcohol and CNS depressant medications were excluded. In addition, abuse/misuse is considered as an

Criteria	Reason for Being an Exclusion Criterion	Is it Considered Missing Information?	Rationale
			important potential risk based on non-clinical findings.
Exposure to another investigational medication or device within 30 days prior to screening.	To avoid confounding the evaluation of safety outcomes	No	The exclusion was not due to a specific safety concern with zuranolone.
Concomitant or previous administration of: • Other allopregnanolone-containing compound. • Benzodiazepines, barbiturates, or $GABA_A$ modulators at Day-28 or daily or near-daily for 1 year, in the last year prior to the first dose of study drug. • Benzodiazepine or $GABA_A$ modulator with a half-life of ≥ 48 hours from 60 days prior to Day 1. • Non-GABA anti-insomnia medications or first generation or second-generation antipsychotics at Day -14. • Psychostimulants or opioids, at Day -28. • Use of any known strong inhibitors of cytochrome P450 (CYP)3A4 or of any strong CYP3A induces within 14 days or 5 half-lives	To avoid confounding the evaluation of safety outcomes and/or efficacy	No	Initiation of new psychotropic medications, including antidepressant or antianxiety medications, and any new pharmacotherapy regimens that may potentially have an impact on efficacy and/or safety endpoints prior to, or during the PPD trials was prohibited. As zuranolone has CNS depressant effects the use with another CNS depressant medicinal product was prohibited in clinical trials. Concomitant use of zuranolone with a strong CYP3A inhibitor increases the exposure of zuranolone. Concomitant use of zuranolone with a CYP3A inducer decreases the exposure of zuranolone which may reduce the efficacy of zuranolone.
Index pregnancy resulted in a miscarriage, still birth, or neonatal/infant death; or participant has terminated parental rights (e.g., child has been placed for adoption).	To avoid confounding the evaluation of efficacy outcomes	No	The exclusion was not due to a specific safety concern with zuranolone. There is no evidence to suggest that the use of zuranolone in these patients leads to a specific safety concern, or a different outcome to previously

Criteria	Reason for Being an Exclusion Criterion	Is it Considered Missing Information?	Rationale
			identified risks, when zuranolone is used according to the product label.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 9.

Table 9: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. As of 30 Apr 2024, 12 pregnancies in women exposed to zuranolone during clinical trials were identified in the Global Safety Database.
Breastfeeding women	Not included in the clinical development programme. The excretion of zuranolone in breast milk of 15 healthy adult lactating women was evaluated in study 217-CLP-114 for 5 days.
Patients with relevant comorbidities: • Hepatic impairment	The effect of hepatic impairment on the PK of zuranolone was evaluated in a dedicated study (217-CLP-108) in which 24 participants with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment in the pre-authorization CDP were exposed to zuranolone. Normal: 6 Mild: 6 Moderate: 6 Severe: 6

Type of special population	Exposure
Patients with relevant comorbidities: • Renal impairment	A dedicated renal study was performed (217-CLP-107), in which 24 participants with mild to severe renal impairment have been identified as receiving zuranolone. Renal function groups are defined based on eGFR, with values of ≥ 90 (normal), 60 to < 90 (mild), 30 to < 60 (moderate), and < 30 (severe) mL/min/1.73m^2. Patients with end stage renal disease were not included in the CDP. Normal: 6 Mild: 6 Moderate: 6 Severe: 6 In addition, 47 (26.7%) participants with mild impairment were exposed to zuranolone within the PPD PC studies. No participants with moderate or severe impairment were enrolled in zuranolone PPD PC studies.
Patients with relevant comorbidities: • Cardiovascular impairment	Not included in the clinical development programme.
Patients with relevant comorbidities: • Immunocompromised patients	Not included in the clinical development programme.
Patients with relevant different ethnic origin	The number and percentage of patients exposed to zuranolone in the preauthorisation safety PPD PC Pool, by race, were: White = 113 (64.2%) Black or African American = 56 (31.8%) Asian = 2 (1.1%) Other = 4 (2.3%)
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The best available estimate of the cumulative number of patients exposed to zuranolone in the postmarketing setting is derived from Biogen sales data, using total sales patients as of the last month of data available. Data are obtained from the Biogen internal sales database, which includes the number of patients on therapy up to the end of each month. All data are available upon request. Individual-level data are not available for precise patient-time calculation. Estimated cumulative patient-months of exposure was calculated by summing the total number of sales patients each month from the start of marketing through the end of the period and multiplying that number by an assumed person-month contribution of 0.5 months. Patient-years of exposure was estimated by dividing the estimated cumulative patient-months by 12 months/year.

SV.1.2 Exposure

Cumulative postmarketing exposure to zuranolone is presented in Table 10.

Table 10: Estimated Cumulative Postmarketing Patient Exposure

Source	**Cumulative: 04 Aug 2023 to 30 April 2024**	
	Number of Patients	**Patient-Years**
RoW	1133	47.2
Total exposed	1133	47.2

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

Potential for misuse for illegal purposes

Zuranolone crosses the blood brain barrier and enhances GABA activity at synaptic and extrasynaptic receptors [Martinez Botella 2017] and has also been shown to increase cell surface expression of $GABA_A$ receptors in in vitro studies [Althaus 2020].

Non-clinical studies were reviewed to assess the potential for drug abuse liability (see Table 2). The non-clinical in vitro and in vivo abuse potential data suggest that the abuse and dependence potential of zuranolone is likely less than, or at most similar to, that of midazolam and chlordiazepoxide. Such results are consistent with other NAS $GABA_A$ receptor PAMs.

The PK of zuranolone following oral administration is characterised by a relatively slow absorption (i.e., T_{max} of approximately 6 hours postdose for the commercial formulation) and moderately long elimination (i.e., approximately 20 hours), indicating a PK profile that is unlikely to be attractive to potential abusers.

Across the clinical studies no reports of misuse, abuse, or diversion of zuranolone have been reported to date. TEAEs of euphoric mood, feeling drunk, feeling of relaxation, feeling abnormal, and inappropriate affect were reported for a small number of participants in the development programme following administration of zuranolone. Euphoric mood was reported in 1 participant (0.6%) receiving zuranolone in the PPD PC studies. Two participants (0.2%) receiving zuranolone experienced euphoric mood in studies in MDD. Overall, somnolence, dizziness, and sedation were the most commonly reported CNS related TEAEs; however, these events alone are not considered to be a sign of abuse potential

Data from clinical studies combined with the physical dependence study results in rats suggests that zuranolone has low physical dependence potential.

During the postmarketing setting as of 30 Apr 2024, no reports of abuse or misuse were identified.

Based on its MoA, non-clinical, and clinical data (including the dedicated human abuse potential study) with zuranolone indicate that the abuse and dependence potential of zuranolone is likely less than, or at most similar to, that of other $GABA_A$ receptor PAMs.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Table 11: Summary of Safety Concerns

Important identified risks	• None
Important potential risks	• None
Missing information	• None

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

  None.

- **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

  – Identified risk(s):

    – Confusional state: There were 2 participants (1.1%) in the PPD PC studies who experienced confusional state on-treatment in the zuranolone group, with no trend noted across zuranolone treatment groups (1.3% [n = 1] in the zuranolone 30 mg group versus 1.0% [n=1] in the zuranolone 50 mg group). No events were reported in the placebo group. There was 1 serious event that was reported in the zuranolone 30 mg group and was severe in intensity. The event led to hospitalization and resolved the same day without sequelae. The remaining event in the 50 mg group was nonserious and moderate in severity. Both events led to zuranolone dose reduction. No events led to treatment discontinuation.

- **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):**

  – Identified risk(s):

    – Somnolence (including sedation): The incidence of participants reporting somnolence was 26.5% (n = 26) in the zuranolone 50 mg, 15.4% (n = 12) in the zuranolone 30 mg and 7.6% (n = 13) in the placebo groups. A similar pattern was observed for the participants reporting sedation, with an incidence of 11.2% (n = 11) in the zuranolone 50 mg group, 5.1% (n = 4) in the zuranolone 30 mg group, and 0.6% (n = 1) in the placebo group. All events in participants receiving

zuranolone were non-serious. Severity of somnolence was predominantly mild (15.3%, n = 27) or moderate (6.3%, n = 11) and for the events of sedation severity was reported as mild (3.4%, n = 6) or moderate (4.5%, n = 8) for the majority of participants receiving zuranolone in any group. One participant (0.6%) experienced a severe event of sedation in the zuranolone 30 mg group. Among participants who received 50 mg, 7.1% (n = 7) of participants had dose reduced or interrupted and 2.0% (n = 2) discontinued zuranolone due to events of somnolence, and 3.1% (n = 3) had dose reduced or interrupted and 1.0% (n = 1) discontinued zuranolone due to the severe sedation. There were no adverse sequelae reported and most events resolved by the end of treatment course without dose reduction, interruption, or cessation.

- Dizziness: The incidence of participants reporting dizziness was 10.8% (n = 19) in the all zuranolone group and 8.2% (n = 14) the placebo group. Across zuranolone groups, a higher incidence in the zuranolone 50 mg group (13.3% [n=13]) than in the zuranolone 30 mg group (7.7%, n = 6) was noted. All events were non-serious, and all participants reported events that were mild (7.4%, n = 13) or moderate (3.4%, n = 6) in severity, with no severe events reported in participants receiving zuranolone at any dose (all zuranolone group). Among participants who received zuranolone, 3.4%, n = 6] had dose reduced or interrupted, all in the 50 mg zuranolone group; however, no participants discontinued zuranolone due to dizziness, in any group. There were no adverse sequelae and most of the events resolved by end of treatment course.

- Potential risk(s):
  - Withdrawal effects: Non-clinical studies in dogs suggest the potential for withdrawal effects as convulsions were noted in the dog 3- month, 9-month, and periodic dosing studies. Data from the dedicated physical dependence studies and recovery periods of repeat dose toxicology studies demonstrate that zuranolone has low physical dependence potential in animals (see Table 2). In clinical studies, the potential for physical dependence following abrupt discontinuation of zuranolone was evaluated using several approaches including analysis with a validated withdrawal scale (PWC-20), analysis of off-treatment follow-up TEAEs, and additional analyses with other assessments potentially related to withdrawal. Overall, there were few off-treatment TEAEs reported in clinical studies of zuranolone. The incidence of off-treatment TEAEs in participants with PPD with increasing dose of zuranolone was similar between the zuranolone and placebo groups (with placebo at a slightly higher incidence overall than any individual zuranolone treatment group). In the PPD PC studies, the most common off-treatment reported TEAEs observed were headache, nausea, and dizziness (headache and dizziness reported at a higher incidence in placebo-treated participants compared with the all zuranolone group). The review of the available clinical data including the physician withdrawal checklist (PWC-20), off-treatment vital signs, and drug discontinuation emergent adverse events, did not support a withdrawal syndrome following abrupt discontinuation of zuranolone. There was 1 event of seizure and 1 event of seizure-like episode in studies in

MDD. However, neither event was consistent with a withdrawal seizure. Given the non-clinical and clinical data available withdrawal effects are considered a potential risk with zuranolone. The 14-day duration of treatment limits the potential for withdrawal effects in clinical practice.

- **Known risks that do not impact the risk-benefit profile:**
  - Potential risk(s):
    - Embryofoetal toxicity: Non-clinical findings were observed in rodent embryofoetal development studies, and in a neurodegeneration study conducted in postnatal rats (see Table 2). Relevance of these changes in humans is unknown. Twelve pregnancies in women exposed to zuranolone were identified in the overall zuranolone clinical development programme, all from studies in participants with MDD. No pregnancies have been reported in zuranolone PPD studies. Outcome was reported for 11/12 of the pregnancies: 6 resulted in live births without congenital anomaly (1 outcome was received after the DLP in a participant who was not exposed to zuranolone during pregnancy), 1 resulted in stillbirth, and the remaining 4 resulted in elective pregnancy terminations. The pregnancy outcome was not reported for 1 participant who was lost to follow-up. In addition, 1 pregnancy was reported in the female partner of a male study participant exposed to zuranolone; the final outcome is unknown since this participant was lost to follow-up. There is no clinical evidence of embryofoetal toxicity; however, the limited pregnancy data preclude meaningful conclusions regarding the safety of zuranolone and pregnancy. A low percentage of pregnancies is expected in the post-partum period [Marinovich 2021; Smith 2003]. The use of zuranolone is contraindicated during pregnancy. This potential risk can be managed in clinical practice by advising that women of childbearing potential have to use effective contraception during treatment and for 7 days following discontinuation of treatment in the SmPC.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The rationale for considering the remaining risks relevant for inclusion in the current list of safety concerns (at the time of initial MAA) is presented in Table 12.

Table 12: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk category	Risk-benefit impact
Important identified risks	• None
Important potential risk	• None
Missing information	• None

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

SVII.2.1 Newly identified safety concerns

Not applicable for initial marketing authorisation application submission.

SVII.2.2 Reclassification of existing safety concerns

Not applicable for initial marketing authorisation application submission.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified risks or important potential risks for zuranolone.

SVII.3.2 Presentation of the missing information

Not applicable. There is no missing information for the use of zuranolone.

PART II: MODULE SVIII - SUMMARY OF SAFETY CONCERNS

The zuranolone safety specification includes the following important identified risks, important potential risks, and areas of missing information (Table 13).

Table 13: Summary of safety concerns

Important identified risks	• None
Important potential risks	• None
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III: 1 Routine pharmacovigilance activities

Biogen employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise any safety concerns discussed in this EU RMP. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

Routine pharmacovigilance of adverse reaction reporting and signal detection is considered sufficient to monitor the product safety profile.

III. 2 Additional pharmacovigilance activities

Not applicable. There are no additional pharmacovigilance activities proposed for zuranolone.

III. 3 Summary table of additional pharmacovigilance activities

Not applicable. There are no additional pharmacovigilance activities proposed for zuranolone.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable - there are no imposed post-authorisation efficacy studies.

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

V: 1 Routine risk minimisation measures

Not applicable.

V. 2. Additional risk minimisation measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR ZURZUVAE (ZURANOLONE)

Summary of Risk Management Plan for Zurzuvae (zuranolone)

This is a summary of the risk management plan (RMP) for Zurzuvae. The RMP details important risks of Zurzuvae, how these risks can be minimised, and how more information will be obtained about Zurzuvae's risks and uncertainties (missing information).

Zurzuvae's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zurzuvae should be used.

This summary of the RMP for Zurzuvae 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 of the Zurzuvae's RMP.

I. The medicine and what it is used for

Zurzuvae is authorised for the treatment of postpartum depression (PPD) in adults following childbirth (see SmPC for the full indication). It contains zuranolone as the active substance, and it is given orally.

Further information about the evaluation of Zurzuvae's benefits can be found in Zurzuvae's EPAR.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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

II.A List of important risks and missing information

Important risks of Zurzuvae are risks that need special risk management activities to further investigate or minimise 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 Zurzuvae. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this 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 (e.g., on the long-term use of the medicine):

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risk(s)
None

Important Potential Risk(s)
None

Missing Information
None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Zurzuvae.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Zurzuvae.

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.