EU Risk Management Plan for RXULTI (Brexpiprazole)

RMP version to be assessed as part of this application:

RMP Version number: 2.1

Data Lock Point for this RMP: 31 Jan 2024

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Rationale for submitting an updated RMP: Due to extension of indication to include treatment of schizophrenia in adolescents aged 13 years and older.

Summary of significant changes in this RMP:

RMP Part / Module / Annex	Significant Changes
Part II /Module SI: Epidemiology of the Indication(s) and target population (s)	Updated with information related to schizophrenia in paediatric population
Part II /Module SII - Non-clinical part of the safety specification	Not Applicable
Part II /Module SIII - Clinical trial exposure	Updated Clinical Trial Exposure
Part II /Module SIV - Populations not studied in clinical trials	Module SIV.3 updated with the data from completed and ongoing paediatric schizophrenia trials
Part II /Module SV - Postauthorisation experience	Updated post-authorisation exposure
Part II /Module SVI - Additional EU requirements for the safety specification	Not Applicable
Part II /Module SVII - Identified and potential risks	In the Module SVII.2 deleted justification for removal of safety concerns provided in the RMP version number 2.0.
Part II /Module SVIII - Summary of the safety concerns	Not Applicable
Part III: Pharmacovigilance Plan (including postauthorisation safety studies)	Not Applicable
Part IV: Plans for postauthorisation efficacy studies	Not Applicable
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Not Applicable
Part VI: Summary of the risk management plan	Updated with information related to schizophrenia in paediatric population
Part VII: Annexes	Not applicable

Other RMP versions under evaluation:

There are no previously submitted versions of this EU RMP that are still under evaluation by the Agency.

Details of the currently approved RMP:

- Version number: 2.0
- Approved with procedure: MAA Renewal, EMEA/H/C/003841/R/0014
- Date of approval (EC decision date): 26 May 2023

QPPV name: Emiel van Heumen, MD, MSc.

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

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List of In-text Tables

List of Abbreviations, Acronyms, and Definition of Terms

Abbreviation/Acronym	Definition
AAD	Agitation associated with dementia of the Alzheimer's type
ADHD	Attention-deficit hyperactivity disorder
ADR	Adverse drug reaction
ADT	Antidepressant Treatment
AE	Adverse event
AESOP	Aetiology and Ethnicity in Schizophrenia and Other Psychoses
ALT	Alanine aminotransferase
ASD	Autism Spectrum Disorder
AST	Aspartate aminotransferase
ASQ	Autism Spectrum Quotient
ATC	Anatomical therapeutic chemical classification system
ATMP	Advanced therapy medicinal product
AUC	Area under the plasma drug concentration (versus time)
CBT	Cognitive Behavioural Therapy
CCDS	Company core data sheet
CCSI	Company core safety information
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CLCr	Creatinine clearance
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CNS	Central Nervous System
CPK	Creatine phosphokinase
DM	Diabetes Mellitus
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
DUS	Drug utilisation study
EEA	European economic area
ECA	Epidemiologic Catchment Area
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPS	Extrapyramidal symptoms
EU	European Union
GPV	Global Pharmacovigilance
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLGT	High level group term
HLT	High level term

Abbreviation/Acronym	Definition
HR	Hazard Ratio
IBS	Irritable bowel syndrome
ICH	International Conference on Harmonisation
IDDM	Insulin-dependent diabetes mellitus
IMP	Investigational Medicinal Product
INN	International nonproprietary name
IRR	Incidence Rate Ratio
LAI	Long Acting Injectable
MAH	Marketing authorisation holder
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum Recommended Human Dose
N/A	Not applicable
NPRAA	National Pregnancy Registry for Atypical Antipsychotics
OCD	Obsessive compulsive disorder
OR	Odds Ratio
PAES	Postauthorisation efficacy study
PASS	Postauthorisation safety study
PCR	Potentially clinically relevant
PL	Package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PT	Preferred term
PTSD	Post-traumatic stress disorder
QPPV	Qualified person for pharmacovigilance
RMP	Risk management plan
SGA	Second-generation antipsychotic
SMR	Standardised mortality ratio
SOC	System organ class
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US	United States (of America)
VTE	Venous Thromboembolism

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Active Substance Information	
Active substance(s) (INN or common name)	brexpiprazole also referred to as • OPC-34712 • OPC 331 • Lu AF41156
Pharmacotherapeutic group(s) (ATC code):	Psycholeptics, other antipsychotics, N05AX16
Name of marketing authorisation applicant	Otsuka Pharmaceutical Netherlands B.V.
Medicinal products to which this RMP refers:	1
Invented name of the product in the European Economic Area (EEA)	RXULTI
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Atypical antipsychotic (ATC N05AX16)
	Summary of mode of action: Brexpiprazole is an atypical antipsychotic agent. Overall, the broad spectrum of brexpiprazole receptor binding profile shows that it has high affinity for multiple monoaminergic receptors including serotonin 5-HT1A, 5-HT2A, 5-HT2B, 5-HT7, dopamine D2, D3, and noradrenergic α1A, α1B, α1D, and α2C receptors. Brexpiprazole acts as a partial agonist at the 5-HT1A, D2, and D3 receptors and as an antagonist at 5-HT2A, 5-HT2B, 5-HT7, α1A, α1B, α1D, and α2C receptors. Dose response occupancy and brain/plasma exposure relationship were determined in vivo or ex vivo for D2/D3, 5-HT2A, 5-HT1A, 5-HT6, and 5-HT7 receptors as well as for the 5-HT transporter.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current: Treatment of schizophrenia in adult patients
	Proposed: Treatment of schizophrenia in adults and adolescents aged 13 years and older.
Dosage in the EEA	Current: For adult population: Recommended starting dosage is 1 mg once daily on Days 1 to 4, taken orally with or without food. Recommended target dosage is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on patient's clinical response and tolerability. Maximum recommended daily dosage is 4 mg.
	Proposed: For paediatric population: The recommended starting dose for brexpiprazole is 0.5 mg taken orally once daily on days 1 to 4.

Table 1-1 Active Substance Information	
	The brexpiprazole dose should be titrated to 1 mg once daily on day 5 through day 7 and then to 2 mg on day 8. Weekly dose increases can be made in 1 mg increments based on clinical response and tolerability. The recommended target dose range is 2 mg to 4 mg once daily. The maximum recommended daily dosage is 4 mg
Pharmaceutical Form(s) and Strength(s)	Current (if applicable): Film-coated tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg
	Proposed (if applicable): Not applicable
Is/will the product subject to additional monitoring in the EU?	No

2 PART II: Module SI-SAFETY SPECIFICATION

2.1 Module SI: Epidemiology of the Indication and Target Population(s)

2.1.1 Indication: Paediatric Schizophrenia

Incidence: Paediatric or childhood-onset schizophrenia is very rare. Population-based incidence data or meaningful data on international variability are sparse. Experts estimate that 4% of schizophrenia arises before 15 years of age (early onset schizophrenia), that 0.5-1% arises prior to age 10, and that 1 in 10,000 children develop schizophrenia[1]. A study of 3,280 children in Hessen, Germany, found that schizophrenia was rare, but less so among children older than 13 years.[2] Another German sample of 280 inpatients at Marburg University Hospital in 1991-1992 included 61 patients with schizophrenia ages 7-21 of whom 32 were male and 29 female. The male to female ratio appeared to be significantly higher in those younger than 13 years of age; again schizophrenia diagnoses were much more common after 13 years of age.[3] A recent meta-analysis of 192 epidemiological studies of mental disorders explored their ages of onset.[4] Among the 25 studies which included schizophrenia, the peak age of onset was found to be 20.5 years. Of these cases, 2.0% had their onset prior to 14 years of age, 8.2% prior to 18 years, and 47.4% by 25 years.

Prevalence: Data on the prevalence rate of early-onset schizophrenia are also sparse. It is estimated that up to 5% of children have psychotic symptoms; it is difficult to estimate what fraction of these develop childhood onset schizophrenia, although some estimates have ranged as high as 30%.[5]

Risk Factors: Multiple risk factors have been identified for schizophrenia, potentially for early onset disease. Family history is a well-established risk factor for schizophrenia.[6] However, in a review of more than 15 studies that reported associations between schizophrenia and familial aggregation, Kendler and Tsuang[7] found that most studies were marred by potential methodologic biases; a careful analysis found no strong evidence of familial risk. On the other hand, twin studies have demonstrated strong evidence of heritability; the incidence rate in monozygotic twins in particular appears to be 50% whether the twins were raised together or not.[8] The same authors conclude that schizophrenia does aggregate in relatives of schizophrenics and that the risk is up to 5-10 times greater than in relatives of control, unaffected probands.

Obstetric complications also likely pose a risk. In a review by Cannon *et al*.,[9] multiple studies suggested positive associations between pregnancy complications, such as bleeding or pre-eclampsia; abnormal fetal growth (e.g., low birthweight); and delivery problems (e.g., the need for a Cesarean section) and subsequently diagnosed schizophrenia. However, given the methodological issues and biases in all these studies, questions remain as to the validity of the increased risks reported.

A case-control study that included all schizophrenia cases diagnosed at 15-21 years of age in Sweden from 1973 to 1979, compared to population-based controls, identified a variety of prenatal and perinatal risk factors. These included multiparity, bleeding during pregnancy, and small size for gestational age among males, and maternal diabetes among females.[10]

Demographics of the Population in the Approved Indication

There is evidence of significant and independent variation in schizophrenia incidence by gender, age, ethnicity, and geographical location. This variability is discussed in detail below.

Gender and Age of Onset: Differences in Incidence

Findings regarding differences in schizophrenia incidence according to gender have been inconsistent. A two year (from 1997-1999) population-based prospective case control study of three centers in England (the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study), ages 16 to 64 years, found the risk of schizophrenia at younger ages to be greater among men than women.[11] The overall ratio of men to women appears to be around 2:1 but the ratio is higher at younger ages, e.g., ages 16-19 years and 20-24 years.[11] As noted previously, the male to female ratio appears to be even higher for younger age groups.

Migrant vs. Native-Born Differences

Evidence, although heterogeneous, consistently reveals that immigrant populations have a higher incidence of schizophrenia than the host country native populations.[12,13] This elevated incidence is particularly apparent for migrants from developing countries to European or Westernised countries; and evidence has indicated that differences in the level of economic development in the region of birth are significantly associated with a heightened risk.[13] A meta-analysis of studies conducted in the UK, Australia, the Netherlands, Sweden, and Denmark) examined the risk of schizophrenia among immigrants, including those from the Caribbean, Africa, West Africa, Morocco, Eastern Europe, India, Pakistan, Asia, and the Middle East. The analysis found that the mean

relative risk of schizophrenia among first- and second-generation migrants compared to native born individuals was 2.9 (95% CI: 2.5 - 3.4). However, the effect sizes varied widely across the included studies and the analysis included no specific data for paediatric age groups.[13]

Other Risk Factors for Schizophrenia

One systematic review of studies published between 1965-2002 showed that incidence rates differed significantly by settings (urban: 19 per 100,000 vs. mixed rural-urban: 13.3 per 100,000).[14] However, this review did not provide data on paediatric schizophrenia. The article suggested that migrants had higher rates than native-born individuals. A meta-analysis of 12 studies showed that season of birth was associated with risk of schizophrenia; winter and spring birthdays were associated with modestly increased risk; this study also did not include paediatric age groups.[15]

Existing Treatment Options

Main treatment options

Antipsychotics are the mainstay of treatment for schizophrenia among children; because of the high morbidity and mortality of untreated schizophrenia, antipsychotics are recommended as first-line treatment in international guidelines.[16] Antipsychotics are also second-line treatment for schizophrenia, and patients frequently switch agents to improve effectiveness or to minimize side effects. Brexpiprazole will be used both first line for the treatment of newly diagnosed schizophrenia in adolescents and as an option when switching treatments among adolescents with schizophrenia who are already taking an antipsychotic but have not responded adequately or have experienced medication side effects.

Types of antipsychotics

Antipsychotic medications are traditionally classified as first- or second-generation drugs. Both first- and second-generation antipsychotic medications show benefit compared to placebo in the paediatric patients. Medications with evidence of efficacy in clinical trials include the first generation antipsychotics chlorpromazine, perphenazine, haloperidol, and loxapine and the second-generation antipsychotics clozapine, aripiprazole,[17] brexpiprazole, lurasidone,[18] olanzapine, paliperidone, quietiapine,[19] and risperidone.

Comparative effectiveness of antipsychotics

No randomized clinical trials lasting more than 12 weeks have directly compared the effectiveness of antipsychotic medications among paediatric schizophrenia patients. Clozapine is reserved for people with treatment-resistant schizophrenia, commonly defined as not having responded to adequate trials of at least two other antipsychotics. This is because clozapine may have unique efficacy[20,21] but is also associated with risk for neutropenia — and, rarely, agranulocytosis — and therefore requires close monitoring.[22] Goals of treatment with antipsychotics include increasing adherence, enhancing safety and adaptive functioning, slowing deterioration, minimization of positive and negative symptoms, and minimization of deleterious antipsychotic side effects, such as weight gain, insulin resistance, hyperlipidaemia, extra pyramidal side effects, and QTc prolongation.[23] In clinical practice, treatment decisions often are driven by the desire to minimize specific side effects rather than a belief in comparative effectiveness (e.g., minimization of weight gain or acne) and the choice of antipsychotic agents for children often relies on data from studies performed in adult populations.

Additional treatment considerations

Poor adherence to antipsychotic medications is common among adults with schizophrenia and may be particularly problematic among adolescents with schizophrenia.[24] Long-acting injectable (LAI) formulations of antipsychotics are available and may be preferred when adherence is a concern.[25] Psychosocial treatment, which may include specific forms of psychotherapy, such as cognitive behavioural therapy (CBT) or social skills training, are common adjuncts to medications and may also include focused vocational training.[26] Psychosocial interventions are often initiated in a first episode of psychosis in children with the goal of a voluntary, graduated transition from the inpatient setting to day or partial hospital programs.[26] The availability of these programs varies widely depending on setting and resources available. Mandated outpatient psychosocial treatment is also a feature of treatment for psychosis in some areas, although the evidence of benefit for court-mandated outpatient treatment programs is mixed.[27]

Expected safety profile

Brexpiprazole has affinity for D2 receptors while also binding serotonin 5-HT1a and 5-HT2a receptors.[27] Extrapyramidal side effects are frequently a treatment-limiting consideration for antipsychotics and depend primarily upon D2 receptor activity; brexpiprazole may have decreased D2 receptor activity compared to aripiprazole.[28]

Natural History of the Condition

Diagnosis of schizophrenia during childhood.

Diagnosis of schizophrenia during childhood is associated with more severe disease and a poorer prognosis compared to disease onset during adulthood. Diagnoses of schizophrenia in children <13 years old are particularly associated with severe disease, and have been linked to genetic conditions, obstetrical complications, and structural brain changes likely to be refractory to medications or other treatment.[5,29]

Mortality associated with childhood schizophrenia.

Direct data on mortality associated with schizophrenia in children are sparse. In adults, schizophrenia has been estimated to result in loss of 15-20 years of life expectancy with a 2-3 fold increased risk for death associated with prevalent schizophrenia, a 3-4 fold increased risk for death associated with incident schizophrenia, and a 7-8 fold increased risk for death associated with a first episode of schizophrenia.[30] Risk for suicide is 10-fold among people with schizophrenia compared to age- and sex-matched general population rates.[30] Overall, schizophrenia among children is likely to entail a substantial increase in the relative risk for death — on the order of 4-8 fold, as is observed for incident schizophrenia in adults — due to violence and self-harm; yet schizophrenia does not contribute substantially to the overall mortality rate among children because it is a rare disorder.

Mortality associated with use of antipsychotics.

Studies in adults have typically found reduced mortality associated with use of antipsychotics.[31] In a U.S. study of over two million users of anti-psychotics (all indications) ages 5 to 24 years old, no excess risk for death was associated with standard-dose antipsychotic use. The study did observe a modest excess risk for death associated with high-dose antipsychotics; however, that association may have been related to confounding by indication (i.e., patients with more severe schizophrenia are likelier to receive higher doses of antipsychotics).[32]

Causes of death

Mortality related to schizophrenia in children is likely to be related to injury, violence, and self-harm, which are the most common causes for death among children and adolescents.[33,34] In adults, additional mortality related to schizophrenia may be due to smoking and cardiovascular disease,[35] but deaths related to smoking or cardiovascular disease are exceedingly rare among children.

Comorbidities

Schizophrenia is frequently comorbid with other psychiatric disorders. Alcohol and substance use disorders are frequently comorbid among adolescents with schizophrenia in what is likely to be a bidirectional relationship: substance use may be a risk factor for a new diagnosis of schizophrenia, and the symptoms of schizophrenia are likely to lead to substance use. The following tables describe the relationship between schizophrenia and specific comorbidities.

Table 2.1.1-1	**Schizophrenia and developmental delay**
Incidence	No incidence data are available.
Prevalence	Developmental delay and autism spectrum disorders are common among children with schizophrenia, especially among those with early-onset schizophrenia (typically defined as schizophrenia diagnosed before the age of 13).[36] • Among 99 adolescents and adults with a first episode of psychosis (median age 25 years old), 4 (4%) had a pre-existing diagnosis of autism. An additional 26% of the population had "very high" autism spectrum quotient (ASQ) scores compared to less than 2% of the overall population.[37] • Autism was considered likely or possible in 7 of 19 children with early-onset schizophrenia.[38] • Autism was present in 7 of 18 (39%) children with early-onset schizophrenia, and 72% of children were felt to have some form of developmental delay involving social, cognitive, motor, sensory, or language function.[39] Autism was present in 3 of 23 (13%) children with early-onset schizophrenia and 60% of children had some form of developmental delay not meeting complete criteria for autism.[40]
Mortality	No mortality data deal with developmental delay among children with schizophrenia.
Co-treatment	No specific co-treatment is available for children with schizophrenia and developmental delay.

Table 2.1.1-2	**Schizophrenia and alcohol and substance use**
Incidence	**No incidence data are available.**
Prevalence	Alcohol and substance use disorders are likely to have a bidirectional relationship with schizophrenia in adolescents, as has been observed in adults.[41] Alcohol and/or substance use is prevalent, occurring in over 50% of adolescents with schizophrenia.[42] The lifetime prevalence of an alcohol use disorder has been estimated as high as 86% among those with schizophrenia.[43]
Mortality	Mortality data related to alcohol/substance use among children with schizophrenia are sparse. Among adolescents and adults with schizophrenia, the presence of a concurrent alcohol use disorder was associated with a 69% increased risk for suicidal ideation and a 38% increased risk for suicide.[44]
Co-treatment	No specific co-treatment is available for children with schizophrenia and with alcohol or substance abuse disorders. Treatment often uses a transtheoretical

Table 2.1.1-2	**Schizophrenia and alcohol and substance use**
Incidence	**No incidence data are available.**
	model with a focus on counselling and stages of change to motivate, reduce harmful behaviours, and introduce new coping skills.[45]

Table 2.1.1-3	**Schizophrenia and comorbid psychiatric conditions**
Incidence	**No incidence data are available.**
Prevalence	Psychiatric disorders, including depression and personality disorders, are highly prevalent among children with schizophrenia. Diagnoses of schizophrenia during childhood have been linked to trauma,[46] including formal diagnoses of post-traumatic stress disorder (PTSD) or physical, sexual, or emotional abuse or neglect. • In a cross-sectional survey of over 4,000 adolescents, 84% of those with psychotic symptoms reported childhood trauma, compared to 63% of those without psychotic symptoms[47] • Among 82 children with early-onset schizophrenia (ages 4 to 15 years), 81 had at least one non-schizophrenia psychiatric diagnosis. Psychiatric diagnoses included attention deficit hyperactivity disorder (84%), oppositional defiant disorder (43%), depression (30%), and separation anxiety disorder (25%).[48] • Mood disorders (most often depression or bipolar disorder) were present in 27 to 83% of children and adolescents with early onset (up to age 16)[49,50] schizophrenia Obsessive-compulsive disorder is frequently comorbid with schizophrenia in children and adolescents; substantial diagnostic overlap often makes these conditions difficult to disentangle[51]
Mortality	No mortality data deal with comorbid psychiatric conditions among children with schizophrenia.
Co-treatment	No specific co-treatment is available for psychiatric conditions that may be comorbid with childhood schizophrenia. Antipsychotic medications may be used to treat both conditions (e.g., to treat schizophrenia and depression) or patients may take multiple medications.

Table 2.1.1-4	**Schizophrenia and metabolic disease**
Incidence	**No incidence data are available.**
Prevalence	Metabolic disease arising during schizophrenia may be the direct consequence of antipsychotic medications or may be accelerated by use of antipsychotics among those with pre-existing risk factors such as obesity. Metabolic disease may include weight gain, insulin resistance, and hyperlipidaemia.
Mortality	No mortality data deal with metabolic disease among children with schizophrenia. Metabolic disease is unlikely to contribute to mortality among children because cardiovascular death is so rare in this population but may add substantial morbidity and poor quality of life (e.g., from weight gain/obesity).
Co-treatment	No specific co-treatment is available for metabolic disease among children with schizophrenia. Metabolic disease may be managed in part by changing dose or type of antipsychotic.

Table 2.1.1-5	**Schizophrenia and extrapyramidal symptoms**
Incidence	**No incidence data are available.**
Prevalence	Extrapyramidal symptoms are common consequences of antipsychotic medications and include tardive dyskinesia, Parkinsonism (tremor, rigidity, bradykinesia, masked facies), dystonia, and akathisia. Aripiprazole in particular has been associated with acute extrapyramidal symptoms among children, with an incidence of up to 17% based on meta-analyses.[52]
Mortality	No mortality data deal with comorbid extrapyramidal symptoms among children with schizophrenia.
Co-treatment	No specific co-treatment is available for extra-pyramidal symptoms among children with schizophrenia. Extra-pyramidal symptoms may be managed in part by changing dose or type of antipsychotic.

2.1.2 Indication: Schizophrenia in adult patients

Incidence: Schizophrenia occurs at a relatively low frequency (approximately 0.7%) but there is substantial variability in incidence rates across international epidemiological studies.[12] Reported incidence rates have shown considerable heterogeneity in terms of gender, age, ethnic group, and study center.[53] The heterogeneity in reported incidence rates of schizophrenia is attributed to methodological differences between studies and difficulties inherent in designing studies to obtain a representative estimate; changes in diagnostic criteria over recent years (e.g., “restrictive” vs. “broad” definition in the diagnosis of schizophrenia); the method of case identification (e.g., assertive outreach vs. hospital based services, or personal interview vs. chart diagnosis); the type of recruitment site (inpatient or outpatient setting); scope of coverage (e.g., all patients vs. inpatients only); and whether incidence was assessed based upon rates of first contact with a mental health centre or on admission rates.[12,54,55,56]

The median incidence rate of schizophrenia from a systematic review of studies published from Jan 1965 to Dec 2002 was 15.2 per 100,000.[14]

A review of 16 international studies conducted from the 1930s through the 1970s found that the annual incidence rate for schizophrenia ranged from 17 per 100,000 (United Kingdom [UK]) to 69 per 100,000 (United States [US]).[56]

Changes in Incidence Rates Over Time:

Reports of a decline in the incidence over past decades have been inconsistent. While some studies report significant declines in incidence of schizophrenia[57,58] others have reported an increase in incidence.[54,59,60,61]

Prevalence: Numerous epidemiological studies have been conducted in various sites worldwide to assess the prevalence of schizophrenia.[56,62,63] There is substantial heterogeneity in reported estimates which likely arises due to factors such as the age distribution of the population, mortality rates, and migration patterns within and between sites.[56,63] While estimates vary considerably, prevalence generally ranges from 4 to 7 per 1,000 persons, depending on the type of prevalence estimate used (point, period, lifetime, or lifetime morbid risk.[14]

A systematic review of 188 studies from 46 countries published from 1965 to 2002 estimated median prevalence values (10% to 90% quartile range) per 1,000 persons:

- Point prevalence (≤ 1 month): 4.6 (1.9 - 10.0)
- Period prevalence (> 1 month and < 12 months):
- 3.3 (1.3 - 8.2)
- Lifetime prevalence: 4.0 (1.6 - 12.1)
- Lifetime morbid risk: 7.2 (3.1 - 27.1).[63]

Risk Factors

Family history is a well-established risk factor for schizophrenia.[6] Potential risk factors include obstetric complications[9,10,64,65]; parental age at conception[10,66,67,68,69]; urban vs. rural residence[12]; prenatal infection[57,70]; and below average premorbid cognitive ability.[71]

Demographics of the population in the approved indication – age, gender, racial and/or ethnic origin and risk factors for the disease: There is evidence of significant and independent variation in the incidence of schizophrenia in terms of gender, age, ethnicity, and geographical location.[53]

Gender and age of Onset Differences in Incidence

Findings have been inconsistent with regard to differences in incidence of schizophrenia according to gender.[72] Analyses of international studies provide evidence for a higher annual incidence rate for men:

- Median male/female rate ratio (10% - 90% percentile) = 1.4 (range 0.9 – 2.4).[12]
- Meta-analysis conducted across 49 studies: male to female incidence risk ratio for schizophrenia = 1.42 (95% CI: 1.30 - 1.56).[73]

A 2-year (1997-1999) population-based prospective case control study of three centers in England (the AESOP study)[53] found the risk of schizophrenia to be greater for men than women at younger ages:

- Incidence rate ratio (IRR) for 20 to 24 year age band = 4.1 (95% CI: 2.0 – 8.5).[53]
- Incidence of schizophrenia for men was approximately 40 per 100,000 per year, compared to approximately 10 per 100,000 per year for women.[53] However, differences disappeared with age.[53]

Evidence for the earlier onset of schizophrenia in men is well established. Earlier onset of schizophrenia in men as compared to women has been widely reported with most studies reporting a 3 to 5 year difference.[72,74,75] Difference in age of onset between the genders persists irrespective of culture, diagnostic criteria used, definition of onset, or age distribution of the general population.[74,75]

Of note, the gender differences in age of onset appear to apply only to sporadic schizophrenia and not to familial cases; the age of onset is similar for both genders in instances where a patient has an affected first degree relative (i.e., where there is "high genetic load").[72,74,75] While most studies report a mean age of onset in the early 20s for men and in the mid to late 20s for women[74,75] evidence suggests that there may be age specific peaks in disease incidence for each gender.[72,75,76,77]

Despite the gender specific differences in incidence and distribution in age of onset, the cumulative lifetime risk of schizophrenia is the same for men and women.[78,79]

In contrast to findings for incidence, lifetime prevalence of schizophrenia is similar for men and women across all studies.[58,80] This unexpected finding might be explained by a shorter duration of illness or a higher mortality rate in men.[58] A better outcome for women with schizophrenia has been consistently reported.[81] Moreover, women have a more favourable overall response to treatment.[72,73,75]

Migrant vs. Native-born Differences

Evidence, although quite heterogeneous, consistently reveals that immigrant populations have a higher incidence of schizophrenia as compared to the host country native populations.[12,13,82,83] This elevated incidence is particularly apparent for migrants from developing countries relocating to European or Westernised countries; and evidence has indicated that the level of economic development in the region of birth is significantly associated with a heightened risk.[13]

A meta-analysis of studies for five countries (UK, Australia, the Netherlands, Sweden, and Denmark) examined the risk of schizophrenia among immigrants, including those from the Caribbean, Africa, West Africa, Morocco, Eastern Europe, India, Pakistan, Asia, and the Middle East. The analysis found that the mean relative risk of schizophrenia for first and second generation migrants compared to native born individuals was 2.9 (95% CI: 2.5 - 3.4).[13] However, there was significant heterogeneity in the effect sizes across the included studies.[13]

Urban vs. Rural Setting and Risk of Schizophrenia

One systematic review of studies published between 1965 and 2002 showed that incidence rates differed significantly by settings (urban: 19 per 100,000 vs. mixed rural urban: 13.3 per 100,000).[14]

Population based studies (Denmark) have revealed an association between urban birth, upbringing, or residence and an increased risk of schizophrenia; however, the underlying causes of the urban rural difference in the occurrence of schizophrenia are not known.[84] Smaller studies have also noted the association.[12,53]

Overall Mortality

It has been estimated that, globally, schizophrenia reduces life expectancy by an average of 10 years.[78] Increased mortality has been widely reported for schizophrenia, a finding that has been substantiated by two meta-analyses that included data from up to nine countries.[85,86] The association between severe mental illness and increased mortality has long been recognised. It is postulated that schizophrenia can trigger a cascade of adverse socioeconomic and lifestyle factors (including poor diet, sedentary lifestyle, tobacco use, alcohol use) that often translate into adverse physical health outcomes, particularly chronic disease mortality.[85,86,87] With regard to mortality risk associated with antipsychotic use, one population based study found that treatment with more than one antipsychotic agent may increase the relative risk of mortality.[86] These findings conflicts with other studies that have found reduced mortality associated with antipsychotic use.[31,88,89,90] Based on historic data, aggregate crude mortality rate from meta-analysis is 189 deaths/10,000 population per year.[85] Aggregate all-cause standardised mortality ratio (SMR) in meta-analysis ranged from 1.51 (95% CI: 1.48 - 1.54) to 1.57 (95% CI: 1.53 - 1.60), or a risk of death 1.6 times higher than expected from the general population.[85,91] The ten year survival rate was 81%.[85] More recent data report higher all-cause SMR; a 2007 systematic review across 37 studies from 25 countries found that the median SMR

for all-cause mortality was 2.58, or a risk of death 2.5 higher than expected from the general population, with the central 80% of all SMRs varying over a 4-fold range.[14,87] A large 2015 UK cohort study found that the all-cause SMR was 3.6 (95% CI: 2.6-4.9).[92]

Natural Death

Historical data report that eighty percent of people with schizophrenia die from natural causes, compared to 97% of the general population.[85] Based on meta-analysis of this historical data, natural death accounts for approximately 60% of the excess mortality of schizophrenia.[85,91] Estimated aggregate SMR for natural death ranges from 1.34 (95% CI: 1.31 - 1.37) to 1.37 (95% CI: 1.34 - 1.41).[85,91] Compared with historical data, more recent data report a higher natural-cause SMR. The natural-cause SMR reported by a large 2015 UK cohort study is 1.7 (95% CI: 1.00 - 2.7).[92] As previously discussed, adverse socioeconomic and lifestyle factors in people with schizophrenia likely account for excess mortality risk, particularly chronic disease mortality.[85,92]

Unnatural Deaths

A large UK cohort study found that the unnatural cause SMR was 13.3 (95% CI: 8.7-20.4).[92] A meta-analysis found that unnatural deaths (accidents, suicide, homicide, other) are significantly increased for men and women with schizophrenia.[85,91] Unnatural deaths accounted for 38% to 41% of the total excess mortality of schizophrenia, with a mortality risk approximately 4.3 times higher than expected from the general population (aggregate SMRs were 4.26 (95% CI: 4.02 - 4.51) and 4.34 [95% CI: 4.12 - 4.57]).[85,91] Both historic and more recent data consistently report suicide as the largest single cause of excess mortality in schizophrenia. A 2007 systematic review reports that among all causes of death, suicide is associated with the highest estimate, with an SMR of 12.9 or risk of suicide 12 times higher than expected from the general population.[90] Historical data report aggregate SMRs of 8.38 (95% CI: 7.84 - 8.94) to 9.00 (95% CI: 8.42 - 9.62).[85] Suicide was significantly higher among men than women and was found to occur at the highest rate in the year following diagnosis.[85] The rate of death from accidents among patients with schizophrenia was twice that of the general population (SMR 2.16; 95% CI: 1.96 - 2.36) and accounted for approximately 12% of excess mortality.[85]

The main existing treatment options:

The main existing pharmacological treatment options for patients with schizophrenia are antipsychotics. These have a well characterised safety profile, with most being associated with metabolic disturbances, weight gain and somnolence to a greater or lesser degree as

well as well-known adverse reactions associated with neuroleptic drugs such as extrapyramidal symptoms and neuroleptic malignant syndrome. These effects are well known to the prescribing physicians and are discussed further in Part II SVII.

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

The potential health risk is premature death due to suicide and comorbid conditions. Risk of suicide death is estimated to be approximately nine to twelve times higher for patients with schizophrenia than the general population.[85,93] Among those experiencing acute agitation, aggressive or violent behaviour presents a risk of harm to the patient, family members, or medical personnel. Moreover, violent or aggressive behaviour in agitated patients is associated with suicidal tendency.[94]

Brexpiprazole will be used in patients who are just starting treatment and in patients who have already used at least one antipsychotic which has not controlled their disease. These latter patients may have metabolic disturbances already as part of their previous treatments and may also have unstable disease with the associated risks of comorbid conditions and premature death related to their adverse socioeconomic and lifestyle factors.

Psychiatric comorbidities:

The epidemiology of psychiatric comorbidities in schizophrenia is summarised in Table 2.1.2-1 to Table 2.1.2-7. Psychiatric comorbidities are common among patients with schizophrenia; however, epidemiological data are very limited and most studies examining prevalence are based on small clinical samples. Moreover, reported rates vary greatly, most likely due to differences in patient samples and diagnostic methods/criteria used.[66,67,68,69,70]

Table 2.1.2-1	**SI-1: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Alcohol/Substance use Disorders**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	The rate of substance abuse diagnosis among schizophrenia patients is three to five times higher than that of the general population.[71,72,80] The US Epidemiologic Catchment Area (ECA) Study prevalence rates for comorbid substance abuse were as follows:[71,80] - 47% for any substance abuse or dependence (nearly three times that of the general population) - 34% for any alcohol diagnosis - 28% for any drug other than alcohol

Table 2.1.2-1	**SI-1: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Alcohol/Substance use Disorders**
	The prevalence of "dual diagnosis" in international studies (Italy, Australia, and Germany) was similar to those of US ECA study.[73] The lifetime prevalence rates ranged from 43% to 60% and alcohol abuse reported considerably more frequently.[71,74] A European cross-sectional study in 2010 (Germany, Greece, Italy, and Spain) reported the following prevalence estimates of substance use among patients with schizophrenia:[75] - 62.7% for smoking - 13.4% alcohol addiction - 13.8% for illicit drug addiction
Mortality	Complications of comorbid substance use disorder in schizophrenia include an increased risk of suicide.[71,80] A large-scale population-based study found that the SMRs for tobacco-related illnesses among patients with schizophrenia were as follows: - all tobacco-related malignant neoplasms (except of the cervix uteri): SMR = 1.3 - for all tobacco-related cardiovascular diseases: SMR = 2.46 - all tobacco-linked diseases (except malignant neoplasm of the cervix uteri): SMR = 2.45.[80] One US-based study using vital statistics data estimated that among patients with schizophrenia, the overall five and ten-year mortality risk was lower in cannabis users than in nonusers (3.1% vs. 7.5% and 5.5% vs. 13.6%, respectively; p = 0.005); and alcohol use was not predictive of mortality (all analyses controlled for symptoms and treatments).[76]
Co-prescribed Medicinal Products	ATC codes N07BB Drugs used in alcohol dependence and N07BB Drugs used in opioid dependence.

Table 2.1.2-2	**SI-2: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Depression**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Recognised as an important and distinct syndrome in schizophrenia[77,78] with reported prevalence rates ranging from 25% to 81% depending on treatment setting, phase of illness, and definition used for diagnosis of depression.[77,79] Clinically significant depression occurred in 15.5% of first admission German patients with schizophrenia, while 'depressed mood' was reported in 38.9%.[78] Nearly 40% of patients with schizophrenia were classified as depressed in a large, multisite, US-based observational study.[79] In a mental health care centre located in the Netherlands, 43% of patients with schizophrenia had depressive symptoms.[81]

Table 2.1.2-2	**SI-2: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Depression**
	A Canadian population-based study reported a lifetime prevalence of 54.2% for depression among patients with schizophrenia, as compared to 7.3 % for the general population.[68] Results of the International Survey of Depression in Schizophrenia, distributed to psychiatrists practicing in a broad spectrum of care settings in Australia, Canada, the US, and 21 European countries, indicated that worldwide depression prevalence is approximately 30% among patients with schizophrenia.[13,77]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC codes N05B Anxiolytics, N05C Hypnotics and sedatives, and N06A Antidepressants.

Table 2.1.2-3	**SI-3: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Generalised Anxiety Disorder**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Reported in approximately 50% of schizophrenia patients.[69,82]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC codes N05B Anxiolytics, N05C Hypnotics and sedatives, and N06A Antidepressants.

Table 2.1.2-4	**SI-4: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Panic Disorder**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Prevalence rates across eight international clinical studies ranged widely from approximately 3% to 43%.[66,67] In a Canadian population-based study, 29.5% of patients with schizophrenia also had a diagnosis of panic disorder, compared to 1.4% of the general population.[83]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC codes N05B Anxiolytics, N05C Hypnotics and sedatives, and N06A Antidepressants.

Table 2.1.2-5	**SI-5: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Obsessive Compulsive Disorder (OCD)**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Prevalence rates across 14 international clinical studies ranged from < 2% to 35%.[66,95] A Canadian population based study reported a lifetime prevalence of 59.2% for obsessive compulsive disorder (OCD) among patients with schizophrenia, compared to 4% for the general population.[83]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC code N06A Antidepressants.

Table 2.1.2-6	**SI-6: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Social Anxiety Disorder**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Reported prevalence varied from 13.3% to 36.3% across six studies of outpatient or inpatient subjects;[66,67] a population-based study found that social anxiety disorder was notably high among patients with schizophrenia compared to the general population with rates of 63.4% and 12%, respectively.[83]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC codes N05B Anxiolytics, N05C Hypnotics and sedatives, and N06A Antidepressants.

Table 2.1.2-7	**SI-7: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Post-traumatic Stress Disorder (PSTD)**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Frequencies ranged from 0% to 3.8% in three outpatient clinical studies.[67,68,69]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC codes N05B Anxiolytics, N05C Hypnotics and sedatives, and N06A Antidepressants.

Somatic comorbidities:

The epidemiology of somatic comorbidities in schizophrenia is summarised in Table 2.1.2-8 to Table 2.1.2-14. Somatic illnesses, both acute (e.g., infections) and chronic (e.g., cardiovascular disease) are more common among patients with psychiatric illness than in the general population, however, prevalence data are limited for specific psychiatric diagnoses. While several serious comorbidities of schizophrenia have been found to be treatment related, or to be exacerbated by treatment, numerous comorbidities are independent of drug effects.[84,96] Approximately 24% - 50% of patients with schizophrenia suffer from at least one comorbid condition, and 18% - 33% suffer from three or more somatic comorbidities.[97,98,99,100] These conditions often go unrecognised or misdiagnosed. Comorbidities among schizophrenia patients may be related to complications of the psychotic disorder itself, patients' socioeconomic status, attempts to self-medicate (e.g., substance abuse)[99] or unhealthy or risky lifestyle behaviours.[85,86]

Table 2.1.2-8	**SI-8: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Cardiovascular Disease**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Cardiovascular disease is common among individuals with schizophrenia; however, only one epidemiological study estimating prevalence was found.

Table 2.1.2-8	**SI-8: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Cardiovascular Disease**
	Risk factors for cardiovascular disease are prevalent in the schizophrenia population (excessive weight [men: 18%; women: 26%], diabetes [10.9%], hypertension [33.2%], smoking [64.1%], dyslipidaemia [68.3%]).[87,88] A Canadian population study reported that individuals with schizophrenia (in comparison to those without schizophrenia) were more likely to report diabetes (12% vs. 5%), obesity (35% vs. 16%), and current smoking (44% vs. 23%). However, after adjusting for socio-demographic and lifestyle variables, there was no longer a significant difference in prevalence of diabetes. Heart disease or stroke was reported to a similar degree by individuals with and without schizophrenia (7% vs. 6%).[89] US-based data for the absolute risk of death from coronary heart disease (CHD) was 50% to 75% for patients with schizophrenia vs. 33% for the general population.[90]
Mortality	Cardiovascular and cerebrovascular diseases contribute substantially to mortality (range: 40% - 50%).[31,91,92,93] A large Finland-based study found that the CHD mortality was markedly higher (Hazard ratio (HR) 2.92, 95% CI: 1.70 - 5.00) for those with schizophrenia in comparison to controls.[94]
Co-prescribed Medicinal Products	ATC codes C10 Lipid modifying agents, B01A Antithrombotic agents, C07 Beta blocking agents, C09A Angiotensin converting enzyme inhibitors (plain), and C08 Calcium channel blockers.

Table 2.1.2-9	**SI-9: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Overweight/Obesity**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Prevalence of obesity among schizophrenia patients in the US and Canada is estimated to range between 40% to 60%, compared to 12% to 30% in the respective general populations.[101,102] While schizophrenia is associated with overweight and obesity, there is little data on the prevalence of obesity in schizophrenia before the widespread use of antipsychotic medications; and reported background prevalence rates (i.e., in drug naïve individuals) may be misleading due to confounding factors.[102,103]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC code A08A Antiobesity preparations (excluding diet products).

Table 2.1.2-10	**SI-10: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Type II Diabetes**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	People with schizophrenia may be at increased risk for type II diabetes due to side effects of antipsychotics and poorer overall health, unhealthy lifestyles, and poorer health care.[104]

Table 2.1.2-10	**SI-10: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Type II Diabetes**
	Epidemiological data are limited with most data on prevalence coming from clinical settings. Reported prevalence of type II diabetes in patients with schizophrenia varies widely from 6% to 36% among studies conducted in various populations and treatment settings.[105,106] Evidence supports that prevalence of diabetes in schizophrenia was significant during the time period preceding the widespread use of atypical antipsychotics.[104] From 1996 to 2001, the trend of increasing prevalence of type II diabetes observed in the US was significantly greater for patients with schizophrenia than for the control population.[107] It is possible that the recent rise could be attributed to the increased use of atypical antipsychotics.[107]
Mortality	Endocrine disorders contribute substantially to mortality.[31,91,92] A UK-based case control study found that Type II diabetes mortality was significantly higher for those with schizophrenia in comparison to controls (relative risk (RR) = 2.2 vs. RR = 1.1)[105]
Co-prescribed Medicinal Products	ATC codes A10A Insulin and analogues, and A10B Blood glucose lowering drugs (excluding insulins such as biguanides and sulfonamide).

Table 2.1.2-11	**SI-11: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Immune/Autoimmune**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Evidence suggests an association between immune dysregulation and pathophysiology of schizophrenia.[108] In particular, altered levels of cytokines and elevated circulating levels of various antibodies have been noted in patients with schizophrenia.[108] Schizophrenia patients or their relatives have been reported to have either higher or lower than expected prevalence of some autoimmune disorders.[109] In a large Danish epidemiologic study, patients with schizophrenia had significantly higher prevalence rates for nine autoimmune disorders (including Grave's disease, celiac disease, acquired hemolytic anaemia, interstitial cystitis) compared to controls (crude incidence rate ratios ranged from 1.9 - 12.5).[109] Another large Danish cohort study found that individuals with schizophrenia had a higher risk of autoimmune diseases in comparison to the general population (IRR = 1.53 (95% CI: 1.46-1.62).[110] Autoimmune diseases developed subsequently in 3.6% of individuals with schizophrenia, and 3.1% of individuals with autoimmune diseases had a family history of schizophrenia.[110] In a large Taiwanese epidemiologic study, patients with schizophrenia had significantly higher risk of Graves' disease (odds ratio (OR) = 1.32), psoriasis (OR = 1.48), pernicious anaemia (OR = 1.71), celiac disease (OR = 2.43), and hypersensitivity vasculitis (OR = 5.00), and significantly lower risk of rheumatoid arthritis (OR = 0.52) when compared to controls.[111]

Table 2.1.2-11	**SI-11: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Immune/Autoimmune**
	A history of any autoimmune disease was found associated with a 45% increase in risk for schizophrenia.[109]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC codes N02 Analgesics, M01 Anti-inflammatory and antirheumatic products, and L04A Immunosuppressants.

Table 2.1.2-12	**SI-12: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Infectious Disease**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Prevalence of HIV infection in psychiatric patients ranged from 3% to nearly 30% in a review of 16 studies.[112] Reported prevalence rates for Hepatitis C Virus (HCV) in psychiatric patients have ranged from 8.5% to nearly 20%.[112]
Mortality	Respiratory and infectious diseases persist as leading causes of natural death among individuals with schizophrenia, with endocrine disorders, cardiovascular and cerebrovascular diseases also contributing substantially to mortality.[31,91,92] A meta-analysis found that estimated SMR for infectious diseases for both genders was 9.44 (95% CI: 8.51 - 10.45), and estimated SMR for respiratory diseases for both genders was 2.30 (95% CI: 2.13 – 2.48)[31,92]
Co-prescribed Medicinal Products	ATC code J05AR Antivirals for treatment of Human Immunodeficiency Virus (HIV) infections (combinations).

Table 2.1.2-13	**SI-13: Schizophrenia: Irritable Bowel Syndrome (IBS)**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Patients with schizophrenia may be at greater risk of IBS. A small study found the prevalence of IBS was 19% among patients with schizophrenia in comparison to 2.5% among an age-matched control patient group.[113,114]
Mortality	No mortality figures were found specific to schizophrenia.
Co-prescribed Medicinal Products	ATC code A03 Drugs for functional gastrointestinal disorders.

Table 2.1.2-14	**SI-14: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Osteoporosis**
Incidence	No incidence figures were found specific to schizophrenia.
Prevalence	Patients with schizophrenia, particularly elderly ones, may have an increased risk of osteoporosis due to additional risk factors, including polydipsia (excessive consumption of fluids) and accompanying polyuria, nicotine addiction, long term neuroleptic treatment, all of which may lead to a reduction of bone mineral density.[115]
Mortality	No mortality figures were found specific to schizophrenia.

Table 2.1.2-14	**SI-14: Incidence, Prevalence, Mortality of Comorbidity in Schizophrenia: Osteoporosis**
Co-prescribed Medicinal Products	ATC codes M05B Drugs affecting bone structure and mineralisation, A11CC Vitamin D and analogues, A12A Calcium, G03C/G03F Estrogens/Progestogens and estrogens in combination, and H05BA Calcitonins.

2.2 Part II: Module SII- Non-clinical Part of the Safety Specification

The pharmacology of brexpiprazole possesses a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the serotonin-dopamine system that combines partial agonist activity at serotonergic $5HT_{1A}$ and at dopaminergic D_2 receptors with antagonist activities at serotonergic $5HT_{2A}$ receptors, with similar high affinities at all of these receptors (K_i: 0.1-0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ receptors with affinity in the same nanomolar K_i range (K_i: 0.2-0.6 nM). The 5 HT_{1A}/D_2 receptor partial agonist activities in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may contribute to its antipsychotic and antidepressant efficacy. No significant cause for concern for humans has been identified in the nonclinical safety studies comprising safety pharmacology, repeated dose toxicity in adult and juvenile animals, genotoxicity, reproductive toxicity, carcinogenicity, local tolerance, photosafety, abuse liability/dependence, and immunotoxicity assessments.

Despite the lower intrinsic activity at the D_2 receptor compared with aripiprazole, the liability for catalepsy (animal model for extrapyramidal symptoms [EPS]) of brexpiprazole was comparable with that of aripiprazole (the ratio of ED_{50} of cataleptogenic activity over ED_{50} of inhibitory effect on apomorphine-induced stereotypy = 6.9 versus 6.9, respectively). In addition, catalepsy liability was less than that of olanzapine and risperidone (3.3 and 1.4, respectively), indicating a lower propensity to induce EPS than other atypical antipsychotics. It should also be noted that the relatively high binding affinity ratio H_1/D_2 ($K_{i\ ratio}$ = 66) of brexpiprazole would suggest a low potential for H_1 related sedation.

In safety pharmacology studies in the rat evaluating effects on the central nervous system (CNS), brexpiprazole at oral doses ≥ 30 mg/kg induced CNS depression as well as a dose dependent decrease in body temperature that are considered related to exaggerated pharmacology of brexpiprazole. No statistically significant changes in respiratory system parameters were observed in dogs at the high dose of 30 mg/kg when compared with vehicle-treated dogs. Decreased blood pressure and prolonged QT/QT_c were noted in the

cardiovascular study in conscious dogs, in the juvenile dog toxicity study as well as on Day 1 of the 4- and 13-week repeated dose toxicity study in the monkey. The observed decreased blood pressure was attributed to a blockade of α_1-adrenoceptors in peripheral blood vessels and considered to be consistent with the pharmacological profile of brexpiprazole. The prolonged QT interval and QT_c were considered possibly associated with a pharmacologically mediated decrease in body temperature although brexpiprazole also showed a potential signal for inhibition of ion channel current in the hERG assay; the IC_{50} value was 0.117 μM. No effect on QT interval or QT_c was observed in conscious dogs at 10 mg/kg. The corresponding C_{max} value at this dose was 1059 ng/mL brexpiprazole which is approximately 5.3-fold higher than the steady state C_{max} value (199 ng/mL) seen in patients at the maximum recommended human dose of 4 mg/day. Furthermore, assessments in the anaesthetised dog showed no effect on TRP at an intravenous dose of 3 mg/kg, suggesting a low potential for proarrhythmic risk. No electrocardiography abnormalities or clinically significant changes in blood pressure were observed in patients treated with brexpiprazole at a daily dose of up to 12 mg/day for 14 days.[116]

Pharmacokinetic data on brexpiprazole showed potential mechanism-based inhibition of CYP3A4 in an in vitro assay with human liver microsomes. However, a clinical drug interaction study using lovastatin as a CYP3A4 probe showed no clinically relevant pharmacokinetic drug interaction.

In the repeated dose toxicity studies with brexpiprazole in rats and monkeys, the principal clinical signs observed were those attributed to pharmacological depression of the CNS (such as tremor, closed/partially closed eyes, hypoactivity, and drowsiness). These clinical observations have been reported for other drugs in this class of atypical antipsychotics, e.g., aripiprazole, olanzapine.[117,118]

Changes in male rat reproductive organs (flaccidity and dilatation of the scrotum; atrophy of seminiferous tubules, prostate glands, and seminal vesicles; degeneration/necrosis of germ cells; decreased germ cells or retention of Step 19 spermatids) at high doses were attributed to increased prolactin secretion, starvation of nutrients, and/or decreased body temperature. Other effects considered to be due to hyperprolactinaemia in the rat, secondary to blockage of dopaminergic receptors, included feminised mammary glands in males, and pseudopregnancy, lobular hyperplasia, and milk secretion in mammary glands of females.

Brexpiprazole showed some positive responses in in vitro genotoxicity tests in mammalian cells (mouse lymphoma assay, and chromosome aberration test). However,

brexpiprazole was negative in the bacterial reverse mutation test and in the in vivo genotoxicity tests (a rodent bone marrow micronucleus test and an unscheduled DNA synthesis assay). Based on the weight of evidence from the battery of genotoxicity studies, brexpiprazole was considered not to represent a genotoxic risk to humans.
In the carcinogenicity study with mice, neoplastic (including adenocarcinoma and adenosquamous carcinoma in the mammary gland and pars distalis adenoma in the pituitary gland) and non-neoplastic findings (in the mammary gland, ovary, uterus, and vagina) were observed in females dosed with 0.75, 2, and/or 5 mg/kg/day brexpiprazole. These dose levels correspond to 0.2- to 1.1-fold the maximum recommended human dose (4 mg) based on exposure (AUC). The mammary tumors are secondary to increased prolactin levels due to functional antagonism at dopamine D_2 receptors. The neoplastic changes observed in the female mice are consistently observed in rodents following chronic administration of antipsychotic drugs[117,118] and have been confirmed to be prolactin-mediated.[119] There were no notable neoplastic or non-neoplastic changes in male mice dosed at up to 5 mg/kg/day. No neoplastic changes were observed in male or female rats at doses up to 10 or 30 mg/kg/day, respectively.

No effect on reproductive function in male rats was noted even at doses where flaccidity and dilatation of the scrotum was evident. In females, however, prolonged diestrus and decreased fertility were observed at doses of 3 mg/kg/day and above. This effect on female fertility was likely mediated by functional antagonistic effects at dopamine D_2 receptors (prolonged diestrus caused by hyperprolactinaemia). In embryo-foetal development studies, no clear signs of foetal malformations were observed in brexpiprazole orally treated rats at clinically relevant exposures based on exposure data in non-pregnant rats. In rabbit, vertebral malformations were seen in 3 fetuses from 2 litters at maternally toxic brexpiprazole oral doses corresponding to exposure approximately 17-fold the maximum recommended human dose (MRHD). In a pre/postnatal development study in rats, low birth weight, decreased viability, and decreased body weight were seen in F1 offsprings at maternally toxic doses (30 mg/kg/day).

Brexpiprazole was photocytotoxic to cultured mammalian cells (BALB/3T3 cells) in vitro, but there was no evidence of phototoxicity in female albino or pigmented mice orally administered brexpiprazole at doses up to 20 mg/kg/day for up to 3 days.

Oral administration of brexpiprazole showed no evidence of potential to induce physical dependence in the rat at doses of up to 70 mg/kg/day (corresponding to mean plasma exposures of 458.2 - 598.9 ng/mL) and was not considered to show reinforcing effects in the monkey at self-administered doses of 0.0125 to 0.05 mg/kg/day.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Safety pharmacology In rats brexpiprazole induced catalepsy (animal model for ability to induce EPS) and tremor at high doses.	The ratio between catalepsy and efficacy higher with brexpiprazole compared to other atypical antipsychotics, indicating a lower EPS risk. EPS-related TEAEs have been shown to have a lower incidence in brexpiprazole-treated patients, compared to those treated with other antipsychotic see Part II SVII)
Safety pharmacology CNS effects including hypoactivity, drowsiness, and partially closed eyes were noted in rats and at high doses.	Nonclinical data suggest a potential risk for sedation with clinical use. However, the incidence of sedation in clinical trials was similar in the brexpiprazole and placebo treated groups.
Safety pharmacology Cardiovascular and haemodynamic toxicity: Decreased blood pressure and prolonged QT interval and QTc were noted in the cardiovascular study.	The suggested mechanism for decreased blood pressure observed is probably via the blockade of the α1-adrenergic receptor in peripheral blood vessels. The prolonged QT interval and QTc were considered possibly associated with a pharmacologically mediated decrease in body temperature. No effect on QT interval or QT_c was observed in conscious dogs at 10 mg/kg. Also, extensive clinical data do not support blood pressure decreases and QTc prolongation as relevant for human use. The potential of QTc prolongations was refuted in a clinical TQT study in doses up to 12 mg brexpiprazole. The cardiovascular risks based on pre-clinical data are therefore not considered as important risks.
Carcinogenicity: In the mouse, notable neoplastic and non-neoplastic findings observed in females at doses up to 5 mg/kg/day. There were no notable neoplastic changes in male mice dosed at up to 5 mg/kg/day and no neoplastic changes in male or female rats at doses up to 10 or 30 mg/kg/day, respectively.	The changes in female mice were considered likely to be mediated by functional antagonistic effects at dopamine D_2 receptors and the resulting increase in prolactin, consistent with the pharmacology of brexpiprazole. These prolactin-mediated endocrine tumours were also observed in rodents with other antipsychotics and their clinical relevance is unknown. None of the mean and median changes of prolactin values observed in clinical studies with brexpiprazole were considered to be clinically meaningful. A search of the brexpiprazole clinical database was conducted for sexual dysfunction- and hyperprolactinaemia-related AEs (e.g., decreased libido, anorgasmia, etc) in subjects with a prolactin elevation > 1 × ULN, as determined by using the following preferred terms: blood prolactin increased, blood prolactin abnormal, hyperprolactinemia, galactorrhoea gynaecomastia, breast swelling, breast enlargement, breast mass, breast tenderness, amenorrhea, oligomenorrhea, anovulatory cycle, and hypomenorrhea. Only 1 sexual function related TEAE was identified, which was an event of libido decreased in the long-term uncontrolled schizophrenia trials.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Reproductive Toxicity: Although dilatation and flaccidity of the scrotum was noted, there was no effect on reproductive function in male rats. Female fertility was slightly impaired at doses ≥ 3 mg/kg/day, likely attributed to functional antagonism at D_2 receptors (prolonged diestrus caused by hyperprolactinaemia). Brexpiprazole was not teratogenic in the rat. In rabbits, vertebral malformations were seen in 3 fetuses from 2 litters at maternally toxic brexpiprazole oral doses corresponding to exposure approximately 17-fold the MRHD. The pre- and postnatal study in the rat showed developmental toxicity in offspring (delayed growth and impaired viability) at maternally toxic doses only.	Based on the weight of evidence from the nonclinical program, brexpiprazole was not teratogenic in rats or rabbits. In rats, no clear signs of foetal malformations were observed in brexpiprazole orally treated rats at clinically relevant exposures. In rabbits, vertebral malformations were seen in 3 foetuses from 2 litters at maternally toxic brexpiprazole oral doses corresponding to exposure approximately 17-fold the MRHD. The incidence of individual skeletal malformations is outside the historical control data of test facility and literature data. However, the incidence of total number of foetuses affected fell within the historical control range reported in literature. In the confirmed cases of exposure to brexpiprazole during pregnancy, there were no events of foetal disorders or congenital abnormalities. However, brexpiprazole is not recommended in pregnancy due to limited data in pregnant women.
Phototoxicity: Although concentrations of up to 10 μM brexpiprazole were photocytotoxic to cultured mammalian cells (BALB/3T3 cells) in vitro, there was no evidence of phototoxicity in female albino or pigmented mice administered orally at doses up to 20 mg/kg/day for up to 3 days.	The in vitro phototoxicity of brexpiprazole is of limited clinical relevance for humans since no evidence of phototoxicity was seen in vivo following administration to albino and pigmented mice.

Of the toxicologically important nonclinical effects of brexpiprazole described previously, the pharmacologically-mediated CNS signs observed at high doses represent a possible risk. However, CNS-related side effects related to treatment with brexpiprazole were similar in incidence to those in the placebo group, and/or were lower in incidence compared to other atypical antipsychotics. In addition, although none of the mean and median changes of prolactin values observed in clinical studies with brexpiprazole were considered to be clinically meaningful, hyperprolactinemia is also a potential risk. Based on the available nonclinical data with brexpiprazole, there is no need for additional nonclinical studies.

2.3 Module SIII: Clinical Trial Exposure

As of the cutoff date (31 Jan 2024), approximately 15173 subjects had been exposed to brexpiprazole in clinical trials.

Distribution of the 15173 subjects by age group and gender, as well as by racial group, is presented below in Table 2.3-2 and Table 2.3-4, respectively.

Clinical trial exposure by duration of exposure and by dose are presented below in Table 2.3-1 and Table 2.3-3, respectively, for 12958 subjects exposed to brexpiprazole in phase 2 and phase 3 trials (all completed and ongoing open-label) as of the data cutoff date 31 Jan 2024, including the following studied indications: schizophrenia (3476), major depressive disorder (MDD) (6629), agitation associated with dementia of the Alzheimer's type (AAD) (1074), attention-deficit hyperactivity disorder (ADHD) (155), post-traumatic stress disorder (PTSD) (748), bipolar disorder (504), autism spectrum disorder (ASD) (104) and borderline personality disorder (268).

Please note the patients in the tables below, in the long-term open-label trials, included subjects who had received brexpiprazole in short-term trials and continued brexpiprazole treatment in open-label trials.

Clinical Trial Exposure by Duration of Exposure

Table 2.3-1 SIII.1: Clinical Trial Exposure to Brexpiprazole by Duration of Exposure (Cumulative and by Indication)				
Duration of Exposure	**Subjects**		**Subject Years of Exposure**	
Cumulative for all indications				
< 4 weeks	12958		6416	
≥ 4 weeks	11553		6368.5	
≥14 weeks	6217		5546.7	
≥26 weeks	4180		4688.8	
≥52 weeks	2126		3436.2	
Total	12958		6416	
	Randomised Blinded Trials		**Long-term, Open-label Trials[a]**	
Duration of Exposure	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
Schizophrenia*				
<4 weeks	2341	277.6	2054	2387.3
≥4 weeks	1786	259.6	1834	2381.0
≥14 weeks	239	101.9	1371	2318.4
≥26 weeks	90	58.5	1170	2239.1
≥52 weeks	16	16.0	870	2035.8
Total*	2341	277.6	2054	2387.3
*Additionally, 151 subjects (19.1 subject-years) from other trials (33113006, 33113008, 33113009)				
MDD Adjunctive Therapy				
<4 weeks	3366	657.5	4275	2228.0
≥4 weeks	3132	647.9	3934	2222.4
≥14 weeks	709	362.7	2945	2078.5
≥26 weeks	210	132.9	2222	1786.8
≥52 weeks	0	0	1165	1165.1
Total*	3366	657.5	4275	2228.0
*Additionally, 145 subjects (16.8 subject-years) from other trials (33113001, 33113002, 33113003)				
AAD				
< 4 weeks	916	168.7	423	90.2
≥4 weeks	872	166.9	403	89.6
≥14 weeks	0	0	102	30.6
Total	916	168.7	423	90.2
Adult ADHD				
≥4 weeks	149	14.9	0	0
Total	149	14.9	0	0
Adult PTSD				
<4 weeks	748	124.7	0	0
≥4 weeks	648	121.0	0	0
≥14 weeks	14	4.2	0	0
Total	748	124.7	0	0
Bipolar Disorder				
< 4 weeks	320	25.2	368	127.8
≥4 weeks	0	0	311	126.1
≥14 weeks	0	0	240	114.8
≥26 weeks	0	0	146	73.0
Total	320	25.2	368	127.8
Borderline Personality Disorder				
< 4 weeks	157	27.6	199	36.2

Table 2.3-1 SIII.1: Clinical Trial Exposure to Brexpiprazole by Duration of Exposure (Cumulative and by Indication)				
Duration of Exposure	**Subjects**		**Subject Years of Exposure**	
≥4 weeks	142	26.6	181	35.9
Total	157	27.6	199	36.2
Autism				
< 4 weeks	58	10.4	95	39.1
≥4 weeks	54	10.4	89	39.0
≥14 weeks	0	0	77	36.9
≥26 weeks	0	0	40	20.0
Total	58	10.4	95	39.1
[a] Included subjects who had received brexpiprazole in short-term trials and continued brexpiprazole treatment in open-label trials				

Clinical Trial Exposure by Age, Group and Gender

Table 2.3-2 SIII.2: Clinical Trial Exposure to Brexpiprazole by Age Group and Gender (Cumulative and by Indication)						
Age Group (Years)	**All indications**					
	M		**F**		**Total**	
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
1-5	2	1.4	1	0.5	3	1.9
6-12	90	34.7	13	2.8	103	37.5
13-15	95	97.4	93	89.6	188	187
16-17	79	82.9	87	113.9	166	196.8
18-65	6041	1999.5	7469	2871.8	13510	4871.3
66-75	234	65.5	320	99.7	554	165.2
>75	217	54.2	432	113.7	649	167.9
Total	**6758**	**2335.6**	**8415**	**3292**	**15173**	**5627.6**

Schizophrenia*								
Age Group (Years)	**Randomised, Blinded Trials**				**Long-term, Open-label Trials[a]**			
	M		**F**		**M**		**F**	
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
13-15	26	2.6	28	2.7	66	100.7	69	95.4
16-17	26	2.5	30	3.0	64	1086.1	79	115.6
18-65	1333	159.8	898	107	1003	542	749	429
66-75	0	0	0	0	10	6.7	11	8.8
> 75	0	0	0	0	2	2.0	1	1.0
Total*	**1385**	**164.9**	**956**	**112.7**	**1145**	**1737.5**	**909**	**649.8**
* Additionally, 151 subjects (19.1 subject-years), 109 males (18-65) and 42 females (18-65) from other trials (33113006, 33113008, 33113009)								

MDD Adjunctive Therapy								
Age Group (Years)	**Randomised, Blinded Trials**				**Long-term, Open-label Trials[a]**			
	M		**F**		**M**		**F**	
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
18-65	1146	202	2066	397.4	1418	766	2808	1447.8

Table 2.3-2 SIII.2: Clinical Trial Exposure to Brexpiprazole by Age Group and Gender (Cumulative and by Indication)

66-75	27	9.4	96	37.7	14	5	26	7.5
>75	7	2.3	24	8.7	2	0.5	7	1.2
Total*	**1180**	**213.7**	**2186**	**443.8**	**1434**	**771.5**	**2841**	**1456.5**

* Additionally, 145 subjects (16.8 subject-years), 44 males (18-65) and 101 females (18-65) from other trials (33113001, 33113002, 33113003)

Bipolar disorder

Age Group (Years)	Randomised, Blinded Trials				Long-term, Open-label Trials[a]			
	M		F		M		F	
	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure
18-65	155	12.2	165	13	183	64.3	185	63.5
Total	**155**	**12.2**	**165**	**13**	**183**	**64.3**	**185**	**63.5**

AAD

Age Group (Years)	Randomised, Blinded Trials				Long-term, Open-label Trials[a]			
	M		F		M		F	
	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure
18- 65	59	11.5	67	12.5	23	4.3	16	3.5
66-75	136	25.9	146	28.1	72	14.9	69	14.1
>75	162	29.1	346	61.6	82	17.7	161	35.7
Total	**357**	**66.5**	**559**	**102.2**	**177**	**36.9**	**246**	**53.3**

Adults ADHD

Age Group (Years)	Randomised, Blinded Trials				Long-term, Open-label Trials[a]			
	M		F		M		F	
	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure
18- 65	76	7.4	79	7.6	0	0	0	0
66-75	0	0	0	0	0	0	0	0
>75	0	0	0	0	0	0	0	0
Total	**76**	**7.4**	**79**	**7.6**	**0**	**0**	**0**	**0**

PTSD

Age Group (Years)	Randomised, Blinded Trials				Long-term, Open-label Trials[a]			
	M		F		M		F	
	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure
18- 65	211	34.8	537	89.9	0	0	0	0
Total	**211**	**34.8**	**537**	**89.9**	**0**	**0**	**0**	**0**

Borderline Personality Disorder

Age Group (Years)	Randomised, Blinded Trials				Long-term, Open-label Trials[a]			
	M		F		M		F	
	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure	Subjects	Subject Years of Exposure
18- 65	29	5.3	128	22.3	38	7.3	161	28.9
Total	**29**	**5.3**	**128**	**22.3**	**38**	**7.3**	**161**	**28.9**

Autism Spectrum Disorder

Age Group	Randomised, Blinded Trials		Long-term, Open-label Trials[a]	
	M	F	M	F

Table 2.3-2	**SIII.2: Clinical Trial Exposure to Brexpiprazole by Age Group and Gender (Cumulative and by Indication)**							
(Years)								
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
1-5	2	0.4	0	0	2	1	1	0.5
6-12	43	7.8	4	0.8	67	27.9	5	2.2
13-15	5	0.8	1	0.2	9	3.3	4	1.2
16-17	3	0.4	0	0	4	2	2	0.7
18-65	0	0	0	0	1	0.3	0	0
66-75	0	0	0	0	0	0	0	0
> 75	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0
Total	**53**	**9.4**	**5**	**1**	**83**	**34.5**	**12**	**4.6**

[a] Contains subjects who had received brexpiprazole in short-term trials and continued brexpiprazole treatment in open-label trials

Clinical Trial Exposure by Dose

Table 2.3-3	**SIII.3: Clinical Trial Exposure to Brexpiprazole by Dose (by Indication)**			
Dose of Exposure	**Subjects**		**Subject Years of Exposure**	
All Indications				
<1 mg	476		55.8	
1 - 3 mg	10461		4258	
>3 mg - ≤ 4 mg	1842		1046.7	
> 4 mg	179		55.5	
Total	12958		5416	
Dose of Exposure	**Randomised, Blinded Trials**		**Long-term Open-label Trials[a]**	
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
Schizophrenia*				
<2 mg	346	28.5	109	102.3
2 - 4 mg	1995	249.1	1861	2271.8
>4 mg	0	0	83	13.2
Total*	**2341**	**277.6**	**2053[#]**	**2387.3**
# One subject from study (14644B) is not included as actual dose received was not available				
*Additionally, 151 subjects (19.1 subject-years) from other trials (33113006, 33113008, 33113009)				
MDD Adjunctive Therapy				
<1 mg	221	17.2	714	310.5
1 - 3 mg	3140	639.6	3561	1917.5
> 3mg	5	0.7	0	0
Total	**3366**	**657.5**	**4275**	**2228.0**
*Additionally, 145 subjects (16.8 subject-years) from other trials (33113001, 33113002, 33113003)				
Adults ADHD				
<1 mg	0	0	0	0
1 - 3 mg	155	15.0	0	0
Total	**155**	**15.0**	**0**	**0**
PTSD				

Table 2.3-3	**SIII.3: Clinical Trial Exposure to Brexpiprazole by Dose (by Indication)**			
Dose of Exposure	**Subjects**		**Subject Years of Exposure**	
All Indications				
<1 mg	476		55.8	
1 - 3 mg	10461		4258	
>3 mg - ≤ 4 mg	1842		1046.7	
> 4 mg	179		55.5	
Total	12958		5416	
Dose of Exposure	**Randomised, Blinded Trials**		**Long-term Open-label Trials[a]**	
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
<1 mg	0	0	0	0
1 - 3 mg	748	124.7	0	0
Total	**748**	**124.7**	**0**	**0**
AAD				
<1 mg	20	3.3	22	3.4
1 - 3 mg	896	165.4	401	86.8
Total	**916**	**168.7**	**423**	**90.2**
Bipolar disorder				
2-4 mg	320	25.2	368	127.8
Total	**320**	**25.2**	**368**	**127.8**
Borderline Personality Disorder				
2-3 mg	157	27.6	199	36.2
Total	**157**	**27.6**	**199**	**36.2**
Autism Spectrum Disorder				
0.25-3 mg	58	10.4	95	39.1
Total	**58**	**10.4**	**95**	**39.1**

[a] Included subjects who had received brexpiprazole in short-term trials and continued brexpiprazole treatment in open-label trials

Clinical Trial Exposure by Racial/Ethnic Origin

Table 2.3-4	**SIII.4: Clinical Trial Exposure to Brexpiprazole by Racial/Ethnic Origin**	
All Indications		
Racial Group	**Subjects**	**Subject Years of Exposure**
Asian	2413	657.4
Black or African American	2399	629.1
American Indian or Alaska Native	88	34.3
White	9791	4067.4
Native Hawaiian or Other Pacific Islander	29	6.8
Middle Eastern	1	0.1
Native American	1	0.1
Mixed	1	0.2
Black and White	1	0.1

Table 2.3-4	**SIII.4: Clinical Trial Exposure to Brexpiprazole by Racial/Ethnic Origin**			
Mixed Race American Indian and Caucasian	1		0.1	
Mixed, Unknown	1		0.1	
Other	432		227.1	
Unknown	15		4.8	
Total	**15173**		**5627.6**	
Racial Group	**Randomised Blinded Trials**		**Long-term, Open-label Trials[a]**	
	Subjects	**Subject Years of Exposure**	**Subjects**	**Subject Years of Exposure**
Schizophrenia*				
Asian	507	54.6	400	229.2
Black or African American	431	64.2	318	148.1
American Indian or Alaska Native	24	2.3	28	18.4
White	1265	182.5	1183	1866.7
Native Hawaiian or Other Pacific Islander	1	0.1	1	0.2
Middle Eastern	0	0	0	0
Native American	0	0	0	0
Black and White	0	0	0	0
Mixed, Unknown	0	0	0	0
Other	113	19.4	123	124.1
Unknown	0	0	1	0.6
Total*	**2341**	**323.1**	**2054**	**2387.3**
* Additionally, 151 subjects (19.1 subject-years) from other trials (33113006, 33113008, 33113009)				
MDD Adjunctive Therapy				
White	2425	525.4	3431	1786.9
Black or African American	291	49.5	477	218
American Indian or Alaska Native	16	2.3	20	7
Asian	529	52.9	291	193.7
Native Hawaiian or Other Pacific Islander	4	0.8	10	2.7
Other	100	26.6	46	19.7
Unknown	1	0	0	0
Total	**3366**	**657.5**	**4275**	**2228**
*Additionally, 145 subjects (16.8 subject-years) from other trials (33113001, 33113002, 33113003)				
Adult ADHD				
White	140	13.7	0	0
Black or African American	9	0.9	0	0
American Indian or Alaska Native	1	0.1	0	0
Asian	3	0.2	0	0
Other	2	0.1	0	0
Total	**155**	**15.0**	**0**	**0**

Table 2.3-4	**SIII.4: Clinical Trial Exposure to Brexpiprazole by Racial/Ethnic Origin**			
AAD				
Asian	267	45.2	167	41.1
Black or African American	22	4.3	8	1.5
White	626	119	248	47.6
Other	1	0.2	0	0
Total	**916**	**168.7**	**423**	**90.2**
Adult PTSD				
Asian	20	3.8	0	0
Black or African American	185	30.9	0	0
American Indian or Alaska Native	12	2	0	0
White	501	82.6	0	0
Native Hawaiian or Other Pacific Islander	6	1.1	0	0
Other	24	4.3	0	0
Total	**748**	**124.7**	**0**	**0**
Bipolar disorder				
Asian	3	0.2	2	0.3
Black or African American	124	8.5	95	24.1
American Indian or Alaska Native	3	0.3	3	1.5
White	184	15.9	266	101.6
Native Hawaiian or Other Pacific Islander	2	0	0	0
Other	4	0.3	2	0.3
Total	**320**	**25.2**	**368**	**127.8**
Borderline Personality Disorder				
Asian	7	1.3	4	0.6
Black or African American	19	3.2	26	4.7
American Indian or Alaska Native	3	0.5	2	0.4
White	122	21.4	159	29.1
Native Hawaiian or Other Pacific Islander	1	0.2	1	0.2
Other	5	1	7	1.2
Total	**157**	**27.6**	**199**	**36.2**
Autism Spectrum Disorder				
Asian	2	0.4	4	1
Black or African American	3	0.6	10	3.3
White	47	8.4	75	31.8
Native Hawaiian or Other Pacific Islander	1	0.2	1	0.5

Table 2.3-4	**SIII.4: Clinical Trial Exposure to Brexpiprazole by Racial/Ethnic Origin**			
Other	5	0.8	5	2.5
Total	**58**	**10.4**	**95**	**39.1**

[a] Contains subjects who had received brexpiprazole in short-term trials and continued brexpiprazole treatment in open-label trials.

Information about paediatric and elderly subjects (age 65 and older) is provided in Section 2.4, which follows.

2.4 Module SIV: Populations Not Studied in Clinical Trials

2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies**		
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Medication Allergy	To protect subjects from serious hypersensitivity reactions	No	Contraindication
Elderly patients (age > 65)	In phase III, schizophrenia studies these patients were not included because some comorbidities and concomitant medications can complicate assessments of safety and efficacy. In addition, safety and efficacy data were collected in clinical studies supporting other indications, e.g. MDD, AAD.	Yes	N/A
Sexually active females of childbearing potential and male subjects who did not agree to stated methods of birth control Females who are breastfeeding and/or who have a positive pregnancy test	To avoid exposure of investigational agent in fetuses or newborns	Yes	N/A

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
result prior to receiving trial drug			
Substance use disorders	To limit confounding factors in the trials	No	Non-clinical studies suggested low potential of brexpiprazole for drug abuse liability and misuse for illegal purposes. In post-marketing experience no evidence of increased risk of drug abuse, misuse and overdose in association with use of brexpiprazole impacting benefit-risk balance of the product was identified.
Insulin-dependent diabetes mellitus (IDDM)	Limit risk of safety related comorbidity	No	Participants with well-controlled insulin-dependent diabetes have been permitted in ongoing brexpiprazole PTSD trials. Post-marketing experience does not indicate any specific safety concerns when used in patients with IDDM.
Subjects presenting with a first episode of schizophrenia Subjects who have been hospitalised > 21 days for the current acute episode Subjects with schizophrenia who are considered resistant/refractory Subjects with a significant current DSM-IV-TR Axis I diagnosis other than schizophrenia	First episode patients or very seriously ill may not be appropriate for investigational agent, and/or exposure to placebo Study population limited to schizophrenia only to reduce heterogeneity and ensure clarity in diagnosis. Excluded potential treatment refractory patients due to potential to confound of efficacy signal	No	Experience with approved antipsychotics does not indicate any specific safety concerns when used in patients with significant psychiatric comorbidities Postmarketing experience will assess responses in other populations that are exposed over time.
Subjects with clinically significant tardive dyskinesia.	Limited risk of comorbidity due to unstable	No	The clinical trials recruited patients with medical and/or neurological illnesses representative of the various populations being studied.

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Subjects with severe akathisia Subjects with hypothyroidism or hyperthyroidism (unless stable) Subjects who currently have clinically significant neurological, hepatic, renal, metabolic, haematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as any history of myocardial infarction, congestive heart failure, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C. Subjects with uncontrolled hypertension, symptomatic hypotension, or orthostatic hypotension Subjects with ischemic heart disease Subjects with epilepsy or a history of seizures Significantly abnormal laboratory	medical/neurological diagnoses		These studies provide a basis for predicting the impact of brexpiprazole on patients with more severe or unstable comorbid conditions than those studied. Post marketing experience will assess responses in other populations that are exposed over time.

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale**
tests, vital sign results, or electrocardiogram (ECG) findings that may impact safety or affect interpretation of results			
Subjects with a significant risk of violent or suicidal behaviour	Use of placebo in trials required exclusion at significant risk for suicide or violent behaviour	No	Experience with approved antipsychotics does not indicate any specific safety concerns when used in patients with significant psychiatric comorbidities Postmarketing experience will assess responses in other populations that are exposed over time.
Subjects receiving CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers . Psychotropic agents and agents with potential CNS effects	To avoid confounding factors on efficacy and safety as brexpiprazole is metabolised through these 2 metabolic pathways. Psychotropic agents were excluded to prevent bias in the efficacy assessment due to effects of these drugs.	No	Drug interaction studies have provided the required information to ensure that patients excluded from Phase III studies may be dosed appropriately with brexpiprazole. Clinically relevant interactions are covered in the SmPC and relevant dose adjustment recommendations are provided.
Prisoners or subjects who are compulsorily detained for treatment of psychiatric or medical condition	Inability to ensure appropriate consent and/or absence of coercion to participate in investigational trial	No	Involuntary detainment may be due to criminal activity or severe disease, but neither are anticipated to impact the safety profile of brexpiprazole.

2.4.2 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.

2.4.3 SIV.3: Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

In the following section, populations who have not been studied in the preauthorisation phase or for which limited information is available from clinical trials will be discussed. Of note, in the Phase II and Phase III safety and efficacy trials in subjects with schizophrenia or MDD, brexpiprazole dose was administered without regard to body weight, metabolism status (CYP2D6), sex, race, or age in adult subjects.

Paediatric Population

For the purpose of extending the therapeutic indication of brexpiprazole to treatment of schizophrenia in adolescents aged 13 years and older, the MAH conducted a multicentre, randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy of brexpiprazole monotherapy for the treatment in adolescents (13-17 years old) with schizophrenia (331-10-234). Additionally, there is an ongoing, open-label extension trial demonstrating long-term safety and tolerability of brexpiprazole monotherapy in adolescent patient population (331-10-236). Safety findings from these studies are summarized below.

- A total of 110 subjects were exposed to brexpiprazole in the trial 331-10-234 (multicentre, randomized, double-blind, placebo- and active-controlled trial to evaluate the efficacy of Brexpiprazole monotherapy for the treatment in adolescents (13-17 years old) with Schizophrenia). The majority of subjects in the Safety Sample were exposed to brexpiprazole for at least 42 days. During the trial at least 1 treatment-emergent adverse event (TEAE) was reported by 44 subjects (40.0%) in the brexpiprazole group. None of the subjects in the brexpiprazole group discontinued the investigational medicinal product (IMP) due to TEAEs. No deaths were reported during this trial. Severe TEAEs were reported in 2 subjects (1.8%) in the brexpiprazole group and 1 subject (1.0%) in the placebo group. Serious TEAEs were reported in 1 subject (0.9%) in the brexpiprazole group, 1 subject (1.0%) in the aripiprazole group, and 3 subjects (2.9%) in the placebo group. Treatment-emergent AEs with an incidence rate of ≥ 5% in the brexpiprazole group and greater than that in the placebo group included nausea

(6.4% versus 3.8% for the placebo group) and headache (6.4% versus 4.8% for the placebo group). There were no consistent clinically relevant findings seen with laboratory parameters (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values during the trial. Overall, the safety results from administration of brexpiprazole in adolescents ages 13 to 17 years with schizophrenia are consistent with the known safety profile of brexpiprazole.

- As of the data cutoff date of Oct-10-2023 in the 331-10-236 (long-term safety and tolerability of brexpiprazole monotherapy in this same adolescent patient population is presented from the ongoing, open-label extension trial), 294 (100%) total subjects were exposed to at least 1 dose of brexpiprazole in the open-label treatment period at a mean daily dose of 2.475 mg for any exposure. Overall, 184 of 294 (62.6%) subjects experienced a total of 448 TEAEs. A total of 56 (57.1%) subjects with prior brexpiprazole, 53 (59.6%) subjects with prior aripiprazole, 62 (71.3%) subjects with prior placebo, and 13 (65.0%) de novo subjects experienced TEAEs. Severe TEAEs occurring in 9 (3.1%) subjects. A total of 9 (3.1%) subjects discontinued the IMP due to an AE, all of which were rollover subjects. There were no deaths in the trial. Overall, a total of 184 (62.6%) subjects reported TEAEs: 56 (57.1%), 53 (59.6%), and 62 (71.3%) rollover subjects that received prior brexpiprazole, prior aripiprazole, and prior placebo, respectively and 13 (65.0%) de novo subjects. The most commonly reported TEAEs occurring at ≥ 5% overall were somnolence and weight increased (31 [10.5%] subjects each), headache (29 [9.9%] subjects), nasopharyngitis (19 [6.5%] subjects), and akathisia (15 [5.1%] subjects). In the conversion phase, somnolence and irritability were the only TEAEs occurring in more than 1 subject (2 [14.3%] subjects each, respectively). There were no consistent clinically relevant findings seen with laboratory parameters (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values during the trial. Overall, as of this interim analysis (data cutoff date: 10 Oct 2023) in adolescent subjects (13 - 17 years old) with schizophrenia, long-term treatment with brexpiprazole was safe and well tolerated.

In addition, the MAH conducted 2 studies 331-201-00148 (multicentre, randomized, double-blind, placebo-controlled trial of Brexpiprazole in treatment of children and adolescents with irritability associated with autism spectrum disorder) and 331-201-00191(long-term safety and tolerability of brexpiprazole monotherapy in children and adolescents with irritability associated with ASD) including total of 210 children and adolescent with irritability associated with ASD. No new safety information emerged from these studies.

Elderly Subjects

As noted in Table 2.4.3-1, elderly subjects were included in two Phase I trials. After administration of a single 2-mg dose of brexpiprazole to elderly (≥ 65 years) and adult (18-45 years) subjects, brexpiprazole exposure (C_{max} and AUC) was similar in both age groups, and brexpiprazole apparent clearance, adjusted for body weight, was found to be similar regardless of age (Trial 331-10-244). Based on the results of the population PK analysis, age was identified as a statistically significant covariate on apparent volume of distribution (Vc/F); the effects of age within the 5th and 95th percentiles (23 years and 61 years) of the population were -19% to +14%. There was no clinically meaningful difference in the incidence of TEAEs due to age. Also, no clinically meaningful changes from baseline occurred in laboratory parameters, vital signs, or ECGs. Based on these findings, adjustment of brexpiprazole dose in the elderly population is not generally needed.

Based on the results of a safety, tolerability and PK trial, once daily oral administration of brexpiprazole (up to 3 mg/day for 14 days) was safe and well tolerated as an adjunct therapy in the treatment of elderly subjects (70 to 85 years old, N = 11) with MDD and brexpiprazole pharmacokinetics in these subjects was comparable to that of the adult subjects with MDD (Trial 331-12-291).
Brexpiprazole has also been studied as an adjunct treatment in elderly subjects with MDD in 1 randomised, double-blind trial (Trial 14571A) and 1 long-term, open-label trial (Trial 16160A). In Trial 14571A and 9 subjects received brexpiprazole. There were no deaths or SAEs.

A total of 132 subjects (mean age 71 years) were enrolled and treated with brexpiprazole in Trial 16160A in patients with MDD. A total of 102 (77.3%) subjects experienced a TEAE. The TEAEs with the highest incidences were fatigue (15%), restlessness (13%) and increased appetite (9.8%) followed by akathisia, weight increased, anxiety, and dizziness (all approximately 8%). A total of 6 subjects experienced SAEs and 1 subject died during the trial after completion of study treatment of events considered unrelated to IMP (acute myocardial infarction and myocardial rupture). Although, an increase in mean prolactin level was seen during the study, predominantly in women (16% of subjects had potentially clinically significant high plasma level for prolactin), there were no consistent clinically relevant findings seen with other laboratory parameters (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values during the trial. Adjunct treatment with brexpiprazole was safe and well tolerated in elderly patients with MDD, treated with 1 to 3 mg/day flexible dose.

A total of 751 geriatric adults (mean age 74.5 years) with Alzheimer's dementia were exposed to brexpiprazole as part of Trials 331-14-283, 331-14-284, and 331-14-213. Exposure occurred during three double-blind, placebo-controlled trials involving agitation related to Alzheimer's dementia. Across the three trials, a total of 51.1% of participants experienced a TEAE. The TEAEs that were reported in at least 2% of the subjects in brexpiprazole and greater than that of the placebo group were nasopharyngitis, urinary tract infection, somnolence, and insomnia. Headache was reported in >5% incidence category in brexpiprazole group (7.6%), however the incidence of headache in placebo group was 9.3%. Serious TEAEs occurred at a rate of 6.4%. Seven deaths occurred during the three trials (6 in brexpiprazole group and 1 in placebo group) with none considered to be related to brexpiprazole. The overall rate of death was 0.9% for brexpiprazole and 0.3% for placebo.

Pregnant or Lactating Women

Safe use of brexpiprazole during pregnancy or lactation has not been established; therefore, use of brexpiprazole in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

A search in the company's safety database for pregnancy cases identified a total of 61 reports cumulatively through 09 Jul 2022 from all the clinical trials for brexpiprazole. Of these, brexpiprazole exposure was reported in 53 case reports. Thirty-three (33) pregnancies were reported in MDD trials, 8 in schizophrenia trials, 8 in PTSD trials and 4 in other indication trials.

A total of 33 pregnancies were reported in MDD trials. As of the data cut-off date (09 Jul 2022), follow-up information was available for 18 of the 33 pregnancies. There were 4 elective abortions, 2 spontaneous abortions, 1 missed abortion and 11 births. Of the 11 births, 8 were reported at term, 1 pre-term delivery and for 2 gestational age at birth was unknown. All the 11 births were reported as uncomplicated deliveries, and no abnormalities were reported for any of the infants. In 12 of the remaining 15 cases, the subjects were either lost to follow-up or no further information was available as of the data cut-off date. Three partner pregnancies were reported: one in the short-term controlled trial 331-10-227, where pregnancy outcome remained unknown as the patient was lost to follow-up, and two in long-term open label trial 331-10-238, where in one report the patient's wife delivered a healthy baby at term and in the other case, pregnancy was evolving well with no problems as per last follow-up information received. A total of 8 pregnancies were reported in schizophrenia clinical trials. As of the data cut-off date (09 Jul 2022), follow-up information was available for 5 of the pregnancies. There was 1

elective abortion and 4 births. Of the 4 births, 1 was reported at term, and for 3 gestational age at birth was unknown. All the 4 births were reported as uncomplicated deliveries, and no abnormalities were reported for any infants. In the remaining 4 cases, the subjects were either lost to follow-up or no further information was available as of the data cut-off date.

A total of 8 pregnancies were reported in PTSD clinical trials. As of the data cut-off date (09 Jul 2022), follow-up information was available for 3 of the 8 pregnancies. There were 3 elective abortions and in the remaining 5 pregnancies, the subjects were either lost to follow-up or no further information was available as of the data cut-off date.

Brexpiprazole use during pregnancy is monitored within the pregnancy registry based at the Center for Women's Mental Health at Massachusetts General Hospital in Boston, United States. There have been no cases of major malformations associated with use of brexpiprazole during the first trimester of pregnancy. The registry is ongoing, however, the current number of subjects enrolled is not large enough to allow the product specific data analysis for brexpiprazole.

The effect of brexpiprazole on labour and delivery in humans is unknown. Parturition in rats was not affected by brexpiprazole.

Brexpiprazole was excreted in milk of rats during lactation. It is not known whether brexpiprazole or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug considering the risk of drug discontinuation to the mother.

Neonates exposed to antipsychotics, including brexpiprazole, during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder. Consequently, new-borns should be monitored carefully.

Women of childbearing potential must be advised to avoid pregnancy while taking brexpiprazole. Female patients of childbearing potential must use highly effective contraceptive methods during brexpiprazole treatment and also for at least 4-5 weeks following the last dose.

Hepatic and Renal Impairment

Subjects with comorbidities such as hepatic or renal disorders were included in phase 1 trials. Subjects with mild, moderate, and severe hepatic impairment, compared with

matched healthy subjects, had 24%, 60%, and 8% higher brexpiprazole AUC_{∞}, and 14%, 26%, and 55% lower brexpiprazole C_{max}, respectively. Overall, the degree of hepatic impairment did not correlate with brexpiprazole AUC_{∞} consistently. Brexpiprazole C_{max} decreased with greater hepatic impairment may be due to a decreased bioavailability with increasing degree of hepatic impairment. Brexpiprazole terminal elimination half-life ($t_{1/2}$) was increased in subjects with any degree of hepatic impairment, compared with matched healthy subjects (Trial 331-09-225). The normal recommended dosing regimen for brexpiprazole is a starting dose of 1.0 mg/day with gradual increases to target doses of 2 mg to 4 mg in patients with schizophrenia, based on clinical response and tolerability. For patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

Subjects with severe renal impairment exhibited a 68% higher brexpiprazole AUC_{∞} compared with matched healthy subjects, while brexpiprazole C_{max} was unchanged. The apparent increase in brexpiprazole AUC_{∞} in subjects with severe renal impairment is likely due to decreased hepatic clearance and CYP isozyme activity. For patients with moderate, severe or end-stage renal impairment (creatinine clearance, CLcr < 60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

Different Disease Severity

In clinical trials conducted with brexpiprazole in subjects with schizophrenia, the population studied was limited to subjects with acute schizophrenia. Subjects with disease severity different from this inclusion criterion, e.g., treatment resistant schizophrenia, have not been included.

CYP2D6 Metabolism Status

Subjects in the PK study population (combined schizophrenia and MDD) were categorised in accordance with their CYP2D6 metabolizing status. The apparent drug clearance (CL/F) in poor, intermediate, and ultra-rapid CYP2D6 metaboliser subjects was estimated to be -32%, -20% and +18% of the value estimated for CYP2D6 EM subjects, corresponding to a +47%, +25%, and -21% change in brexpiprazole exposure (AUCτ) in these subjects, respectively. No clinically meaningful difference in the incidence of treatment-emergent adverse events (TEAEs) has been observed due to CYP2D6 metabolism status. The normal recommended dosing regimen for brexpiprazole is a starting dose of 0.5 mg/day with gradual increases to target doses of 2 mg to 4 mg in patients with schizophrenia, based on clinical response and tolerability. However, it is recommended that CYP2D6 poor metabolisers and those taking medications that inhibit

either CYP2D6 or CYP3A4, take only half a normal recommended dose. In MDD studies, brexpiprazole was administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). For patients with both impaired CYP2D6 and impaired CYP3A4 metabolisms, whether caused by genotype or drug induced, only one-quarter of a normal dose is recommended.

Table 2.4.3-1 SIV.3-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	No pregnant or lactating women were enrolled in the brexpiprazole clinical trial programme. However, a total of 53 exposures during pregnancies have been reported in all brexpiprazole clinical trials, of which, 33 pregnancies were reported in MDD trials, 8 in schizophrenia trials, 8 in PTSD trials and 4 in other indication trials.
Paediatric subjects	<12 years: 76 subjects and 36.3 subject-years 12-15 years: 169 subjects and 188.8 subject-years 16-17 years: 163 subjects and 194.8 subject-years ≥18 years: 17 subjects and 18.4 subject-years
Elderly persons	MDD 65-74: 110 subjects and 40.9 subject-years 75-84: 41 subjects and 13.4 subject-years >=85: 2 subjects and 0.3 subject-years Healthy Subjects 65-74: 20 subjects and 0.1 subject-years 75-84: 4 subjects and 0.0 subject-years AAD 751 subjects and 196.5 subject-years Groupings by age for AAD population only available for Trial 331-14-213 <64: 24 subjects 65-74: 83 subjects 75+: 121 subjects
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Renal impairment: 10 subjects, 0.0 subject-years Hepatic impairment: 22 subjects, 0.1 subject-years
CYP2D6 metabolizer status (based on population PK analysis of patients from MDD and schizophrenia studies)	Poor: 71 subjects, 7.0 subject-years Intermediate: 580 subjects, 54.3 subject-years Extensive: 929 subjects, 83.4 subject-years Ultra rapid: 51 subjects, 4.8 subject-years

2.5 Module SV: Postauthorisation Experience

2.5.1 SV.1: Postauthorisation Exposure

2.5.1.1 SV.1.1: Method Used to Calculate Exposure

A summary of the worldwide unit distribution of brexpiprazole for the cumulative period from market introduction to 31 Jan 2024 is provided below. Estimates of patient exposure are also provided.

Patient exposure estimates are based on calculations from product distribution figures, and due to the limitations of this approach, it is not possible to reliably estimate the number of subjects treated with marketed brexpiprazole.

To estimate the number of patient-years of treatment, the total number of units distributed at each strength has been divided by 365. It is assumed, therefore, that each patient takes one tablet of brexpiprazole daily.

2.5.1.2 SV.1.2: Exposure

A cumulative summary of the worldwide unit distribution of brexpiprazole from market introduction is provided in Table 2.5.1.2-1, below. Please note that these exposure figures have been calculated from sales data provided through 31 Dec 2023, and include all indications for which brexpiprazole is approved worldwide (i.e., schizophrenia, MDD and agitation related to Alzheimer's dementia).

Table 2.5.1.2-1 SV.1.2-1: Estimated Cumulative Postauthorisation Patient Exposure Units Distributed and Patients Exposed/Patient Years of Treatment for Brexpiprazole through 31 Dec 2023

Strength	Total Number of Units Distributed	Number of Patient-Years of Treatment
0.25 mg	CCI	
0.5 mg		
1 mg		
2 mg		
3 mg		
4 mg		
Total		

Table 2.5.1.2-2 Summarizes the exposure by region worldwide.

Table 2.5.1.2-2 SV.1.2-2: Estimated Postmarketing Patient Exposure by Region through 31 Dec 2023

Region	Exposure (number of tablets sold)	Exposure (Patient Years)
Europe[1]	CCI	
Japan		

Table 2.5.1.2-2	**SV.1.2-2: Estimated Postmarketing Patient Exposure by Region through 31 Dec 2023**	
Region	**Exposure (number of tablets sold)**	**Exposure (Patient Years)**
North America[2]	CCI [redacted]	
Rest of World[3]		
Total		

[1]Europe: comprises the EU and EEA countries Czech Republic, Denmark, Finland, Italy, Netherlands, Norway, Slovenia.
[2]North America: includes Canada and the United States
[3]Rest of World includes: Argentina, Australia, Brazil, Chile, Hong Kong, Indonesia, Israel, Kuwait, Malaysia, Mexico, Panama, Philippines, Russian Federation, Saudi Arabia, Singapore, South Africa, Taiwan, Thailand, Ukraine and United Arab Emirates.
NOTE: Panama also distributes to additional Central American Countries (Costa Rica, Honduras, El Salvador)

There is no data available relating to patient exposure in special populations.

2.6 Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Brexpiprazole showed neither a potential to produce physical dependence in rats nor a reinforcing effect in rhesus monkeys. While the clinical trials did not demonstrate any tendency for drug-seeking behaviour, these observations were not systematic, and it is not possible to predict on the basis of this limited experience, the extent to which a CNS-active drug will be misused, diverted, or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be monitored closely for signs of brexpiprazole misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behaviour).

In a drug abuse liability study in rats, no withdrawal signs suggestive of physical dependence were evident following 4 weeks of brexpiprazole dosing in the diet. Brexpiprazole is not considered to have potential to produce physical dependence. The incidence of subjects who reported ≥ 1 TEAE in the 30-day follow-up period was 2.9% in the all brexpiprazole + Antidepressant Treatment (ADT) group and 3.8% in the placebo + ADT group, and each TEAE reported occurred in 1 subject per treatment group. In the long-term, open label trials, the incidence was 5.1%, and the 2 most frequently reported TEAEs were anxiety (n = 10; 0.5%) and depression (n = 8; 0.4%). There was no indication of a withdrawal syndrome attributable to brexpiprazole.

Brexpiprazole is a prescription only medicine. Limited pack sizes have been designed to restrict access for potential misuse.

Although available preclinical data did not support potential for misuse for illegal purposes, atypical antipsychotic diversion, misuse and even dependency syndrome have been reported in literature and may be considered a class effect.

In the post-marketing experience, no evidence of increased risk of drug abuse, misuse and overdose in association with use of brexpiprazole impacting the benefit-risk balance of the product has been identified.

2.7 Module SVII: Identified and Potential Risks

2.7.1 SVII.1: Identification of Safety Concerns in the Initial RMP Submission

The safety concerns identified for brexpiprazole in the initial RMP submission are described in the sections below.

2.7.1.1 SVII.1.1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

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

Known class risks that are followed up via routine pharmacovigilance, and for which the risk and risk minimisation is understood by prescribers:

The following risks are considered pharmacological class effects for atypical antipsychotics.

Source: Module 2.7, Summary of Clinical Safety; Module 5.3.5.4, MDD Summary of Safety Data

- **Extrapyramidal symptoms (EPS)**
    - For the schizophrenia indication, the percentage of subjects who reported ≥ 1 TEAE associated with EPS in the short-term, controlled trials was 12.0% in the brexpiprazole 2 to 4 mg/day group compared with 9.6% in the placebo group. Akathisia was the most frequently reported EPS-related TEAE in the brexpiprazole 2 to 4 mg/day group (5.6% compared with 4.5% in the placebo group), followed by tremor (2.7% compared with 1.2% in the placebo group). The incidence of dystonia was lower in the brexpiprazole 2 to 4 mg/day group (0.4%) compared with placebo (0.8%)
    - In the MDD short-term controlled trials: All brexpiprazole+ADT group versus placebo+ADT: EPS TEAE (14.3%); placebo (6.4%); Akathisia: (8.5%); placebo (3.2%); Parkinsonian-like events: (5.1%); placebo (2.6%) In fixed-dose trials, the incidence of akathisia in the brexpiprazole+ADT groups was dose dependent; the incidence was similar among the brexpiprazole+ADT dose groups for other EPS-related events. Brexpiprazole 3 mg+ADT group versus placebo: EPS TEAE (18.3%);

placebo (12.2%); Akathisia (13.5%); placebo (5.5%); Parkinsonian-like events (5.7%); placebo (5.5%).

- Extrapyramidal symptoms are addressed in Section 4.4 and 4.8 of the proposed SmPC.

- **Seizure**
  - For schizophrenia, TEAEs related to seizure were reported in a total of 5 subjects: 2 subjects (0.2%) in the brexpiprazole 2-4 mg group, 2 subjects (0.2%) on placebo, and 1 subject on aripiprazole. In the long-term open-label trials, one subject had a non-serious TEAE of seizure leading to discontinuation of IMP. In the long-term controlled trial, no TEAEs associated with seizure were reported in the double-blind maintenance phase. During the stabilisation phase, 1 TEAE of convulsion was reported in a subject receiving brexpiprazole 4 mg/day. The subject recovered and continued in the trial.
  - For MDD, frequencies in short-term trials, 1 (0.1%) in the all brexpiprazole+ADT group, 0 (0%) in the placebo+ADT group. In the long-term controlled trial, 1 (0.2%) in the brexpiprazole+ADT group, 0 (0%) in the placebo+ADT group. In long-term open-label trials, 1 (0.05%) in the all brexpiprazole group. No events were reported from brexpiprazole + ADT group in ongoing trials.
  - Seizure is addressed in Section 4.4 and 4.8 of the proposed SmPC.

- **Suicidality**
  - For the schizophrenia indication, TEAEs related to suicidality in the short-term trials included: 8 subjects (0.5%) in the all brexpiprazole group; 4 subjects (0.3%) in the 2-4 mg brexpiprazole group; 3 subjects (0.4%) in the placebo group. In the long-term controlled trial two subjects (1.9%) in the placebo group experienced suicidal ideation during the double-blind maintenance phase of the trial; there were no reports of TEAEs associated with suicidality in the brexpiprazole group. In the long-term open-label trial, a TEAE related to suicidality was reported for 23 subjects (1.6%).
  - In MDD, in short-term controlled trials, TEAEs related to suicidality were reported for 2 subjects (0.2%) in the all brexpiprazole+ADT group, and 1 subject (0.1%) in the placebo+ADT group. In long-term open label trials, 40 subjects in on brexpiprazole experienced such a TEAE (1.93%). In the long-term controlled trial, 4 subjects (0.9%) in the brexpiprazole +ADT group experienced a TEAE related to suicidality.
  - While spontaneous cases reporting completed suicide and suicide attempt were reported in the postmarketing setting, the majority of these reports included minimal information which precluded a meaningful causality assessment. Furthermore, increased risk of suicidality itself is associated with underlying psychotic disorders.

- Suicidality is addressed in Section 4.4 of the proposed SmPC; suicidal ideation and suicide attempt are described in Section 4.8.

- **Dyslipidaemia**
  - In the schizophrenia short-term controlled trials, 8 subjects (0.7%) in the 2-4 mg brexpiprazole group and no subjects on placebo experienced a TEAE of dyslipidaemia. In the long-term open label trials, TEAEs related to lipids were reported by 13 subjects (0.9%), including 2 events of dyslipidaemia in 2 subjects (0.1%). No subject was discontinued from IMP due to a TEAE related to lipids. In the maintenance phase of the long-term controlled trial, no subjects in either treatment group developed metabolic syndrome. The percentages of subjects who developed dyslipidemia or had elevated fasting glucose (≥ 110 mg/dL) were generally comparable across treatment groups.
  - In the MDD indication, TEAEs of dyslipidaemia occurred in 18 (1.4%) subjects in the brexpiprazole+ADT group in short-term trials, compared with 6 subjects (0.6%) on placebo+ADT. For long-term open-label trials, events were observed in 45 subjects (2.18%) in the brexpiprazole+ADT group. In the long-term controlled trial, 2 subjects (0.5%) in the 1-3 mg brexpiprazole+ADT group experienced TEAEs, compared with 4 subjects (0.9%) on placebo+ADT.
  - Dyslipidaemia is addressed in Section 4.4 of the proposed SmPC.

- **QT prolongation**
  - New onset QTcF interval > 500 msec was not observed in clinical trials with brexpiprazole for either the schizophrenia or MDD indication.
  - Results from a thorough QT trial demonstrated no prolongation of individually placebo- and time-matched corrected QT interval and placebo- and time-matched QTcF following therapeutic (4 mg) or supratherapeutic (12 mg) doses of brexpiprazole.
  - The few observed postmarket cases of 'Electrocardiogram QT prolonged' each present limited information with confounding histories of cardiac events and concomitant medications, cosuspect medications, or unknown medical and past drug histories, from which a causal relationship with brexpiprazole cannot be established.
  - QT prolongation is addressed in Sections 4.4, 4.8, and 5.1 of the proposed SmPC.

- **Creatine phosphokinase (CPK) increase**

- In the schizophrenia indication, the rates of PCR elevations of CPK in the short-term trials were 7.7% in the brexpiprazole group and 5.5% in the placebo group.
- For MDD, the rates of PCR elevations of CPK in the short-term trials were 3.5% in the brexpiprazole +ADT group and 1.8% in the placebo +ADT group.
- Minor mean elevations in CPK were associated with brexpiprazole in the schizophrenia programme. Most events were observed at a single time point and not associated with clinical symptoms of rhabdomyolysis. Rhabdomyolysis was reported as a TEAE in 4 subjects in the short-term schizophrenia trials; 2 in the brexpiprazole 2 to 4 mg/day group, 1 in the brexpiprazole < 2 mg/day group, and 1 in the aripiprazole group. None of the CPK mean changes in the MDD programme were considered to be clinically meaningful.
- The few observed postmarket cases of rhabdomyolysis preclude meaningful assessments that would support a clear causal association with brexpiprazole treatment, due to limited information regarding time to onset (in one case) as well as possible confounding event of fall (in a second case).
- Blood creatinine phosphokinase Increased is included as an ADR in Section 4.8 of the proposed SmPC.

- **Leukopenia, neutropenia and agranulocytosis**
  - In the schizophrenia indication, the mean changes from baseline at last visit for each hematology parameter were small across all treatment groups. In the short-term trials the rates of potentially clinically relevant decreased neutrophils (absolute) and white blood counts were low for brexpiprazole (4 of 1536 subjects and 18 of 1670 subjects, respectively) and placebo (1 of 545 and 10 of 693, respectively). In the long-term trials, 2 subjects had transient leukopenia returning to normal under continued IMP treatment. One subject had TEAEs of leukopenia and neutropenia. There were no reports of agranulocytosis.
  - In the MDD indication, the mean changes from baseline at last visit for each hematology parameter were small across all treatment groups. In the short-term trials the rates of potentially clinically relevant decreased neutrophils (absolute) and white blood count were low for adjunctive brexpiprazole (3 of 1298 subjects and 4 of 1297 subjects, respectively) and placebo (4 of 913 and 3 of 914 subjects, respectively). In the long-term trials, 1 subject had transient neutropenia that returned to normal on treatment and 1 subject had neutropenia before receiving study drug. There were no reports of agranulocytosis or leukopenia in the short-term or long-term MDD trials.
  - In study populations for both indications, there was no evidence suggesting brexpiprazole-related effects on white blood cell (WBC) counts

or neutrophil counts. This was based on the minimal mean changes similar to placebo in short-term trials and the low rates of potentially clinically relevant decreases at any visit, which were always transient.

- Leukopenia, neutropenia and agranulocytosis are addressed in Section 4.4 of the proposed SmPC.

- **Orthostatic hypotension and syncope**
  - In schizophrenia, the incidence of orthostatic hypotension related adverse reactions in brexpiprazole treated patients compared to placebo patients included: dizziness 2.3% vs. 1.4%, syncope 0.1% vs. 0.0%, orthostatic hypotension 0.3% vs. 0.1%, respectively.
  - In MDD, the incidence of orthostatic hypotension related adverse reactions in brexpiprazole+ADT-treated patients compared to placebo+ADT patients included: dizziness 2.5% vs. 1.4%, syncope 0.1% vs. 0.4%, orthostatic hypotension 0.1% vs. 0.0%, respectively.
  - Orthostatic hypotension occurred at similar rates in the brexpiprazole groups as in the placebo groups, and was transient in nature.
  - Orthostatic hypotension and syncope are addressed in Section 4.4 of the proposed SmPC; orthostatic hypotension is also included as an ADR in Section 4.8.

- **Venous thromboembolism (VTE)**
  - In the schizophrenia indication, there were 2 TEAEs related to VTE in short-term trials (deep vein thrombosis and pulmonary embolism) that occurred in the same subject 13 days after brexpiprazole was discontinued. Both events resolved on treatment. Because the events occurred after drug discontinuation, they were assessed as not related to brexpiprazole.
  - In the MDD indication, a TEAE of subclavian vein thrombosis was reported for no subjects in the brexpiprazole+ADT group and 1 subject (0.1%) in the placebo+ADT group in short-term trials. Five (0.24%) subjects had TEAEs for VTE in the long-term open-label trials.
  - Venous thromboembolism is addressed in Section 4.4 and 4.8 of the proposed SmPC.

- **Somnolence and related events**
  - TEAEs related to somnolence in brexpiprazole short-term, controlled schizophrenia trials were reported in 54 subjects (4.5%) in the brexpiprazole 2 to 4 mg/day group compared with 28 (3.8%) subjects in the placebo group. In MDD, these TEAEs were reported in 4.5% of brexpiprazole-treated subjects compared with 1.9% of subjects on placebo in short-term trials. In long-term open-label trials, TEAEs related to somnolence were reported in 13.4% of brexpiprazole+ADT subjects.

- Overall, somnolence was uncommon in MDD controlled trials and the vast majority of cases were mild or moderate in severity. In schizophrenia trials, somnolence occurred at a similar rate as placebo.
- Sedation referenced in Section 4.7 and is listed as a common ADR in Section 4.8.

2.7.1.2 SVII.1.2: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Weight gain	
Clinical and Risk-Benefit Impact	Antipsychotics have been associated with metabolic changes, including weight gain and dyslipidaemia. Metabolic adverse effects can contribute to the increased risk of cardiovascular mortality observed in schizophrenia patients. In clinical trials, weight gain has been observed with brexpiprazole, and a higher frequency of weight increased has been observed with longer exposure. As such, its related impact on risk of obesity and metabolic disturbances cannot be ruled out. Post-marketing data will be used to further characterize events of weight gain experienced with brexpiprazole.
Important Potential Risk: Hyperglycaemia	
Clinical and Risk-Benefit Impact	Hyperglycaemia is considered a class effect for SGAs that have the potential to increase the risk of glucose metabolism disorders in schizophrenic patients. Data to date from the brexpiprazole clinical development programme did not exclude the possibility of an increased hyperglycaemia risk in long term use with brexpiprazole. Metabolic adverse effects can contribute to the increased risk of cardiovascular mortality observed in schizophrenia patients. Extreme cases of hyperglycaemia can be associated with ketoacidosis or hyperosmolar coma or even death. Post-marketing data will be used to further characterize events of hyperglycaemia experienced with brexpiprazole.
Important Potential Risk: Neuroleptic Malignant Syndrome	
Clinical and Risk-Benefit Impact	Neuroleptic malignant syndrome (NMS) is rare, life-threatening adverse event that is considered a class effect for antipsychotic agents, with an estimated incidence of less than 1 case every 1.000 patients per year for SGAs. Although there has been no evidence, either in the clinical development programme or in the post marketing setting, of an increased risk for individuals treated with brexpiprazole, brexpiprazole may have the pharmacodynamic potential to induce NMS as with other SGAs with similar receptor-binding profile. Additionally, the experience with brexpiprazole is limited to date, and possible atypical clinical presentation of NMS may represent a diagnostic challenge. As it is possibly life-threatening and possibly resulting from the long-term use of atypical antipsychotics such as brexpiprazole, it is not currently possible to predict the impact of NMS on the risk-benefit balance of brexpiprazole. Post-marketing data will be used to further characterize events of NMS experienced with brexpiprazole.

Important Potential Risk: Hyperprolactinaemia and Related Disorders	
Clinical and Risk-Benefit Impact	According to a non-clinical carcinogenicity study, brexpiprazole has the potential to induce pituitary and mammary gland degenerative changes, but the potential risk in human is not known. In the clinical setting, observed elevations in prolactin were not considered clinically meaningful. Although there were mostly mild elevations of prolactin in clinical trials, more so in females, these elevations were not associated with clinical symptoms related to hyperprolactinaemia and in general these elevations were transient. In the postmarketing setting, although events such as galactorrhea and menstrual irregularities have been reported, the information to assess any causal relationship has been limited or has been confounded by medical history or concomitant medications. While relevant adverse events to hyperprolactinaemia have been infrequently reported with brexpiprazole, there is currently limited exposure both in the clinical development programme and post-marketing experience to date. Post-marketing data will be used to further characterize events of hyperprolactinaemia and related disorders experienced with brexpiprazole.
Missing Information: Use in pregnancy and lactation	
Clinical and Risk-Benefit Impact	There is limited amount of data from the use of brexpiprazole in pregnant women. Pregnant women have been excluded from clinical trials with brexpiprazole due to uncertainties of the drug's potential effect on the foetus and pregnancy outcomes. Further data collection is therefore warranted. In animal reproduction studies, brexpiprazole was not teratogenic and did not cause adverse developmental effects in developmental toxicity studies. In rats administered brexpiprazole at a maternally toxic dose of up to 30 mg/kg/day, brexpiprazole had no effect on the number of live foetuses, the incidence of external anomalies, or the incidence of malformations and variations. In the rabbit study an oral dose that induced severe maternal toxicity (150 mg/kg/day, AUC exposure 8-fold clinical exposure) was associated with decreased foetal body weight. Visceral and skeletal malformations observed at this dose were similar in incidence to historical control. It is unknown whether brexpiprazole or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of brexpiprazole in milk of rats. A risk to the new-born infants cannot be excluded. Brexpiprazole is not recommended during pregnancy and in women of childbearing potential not using contraception. Because data are limited regarding this use of brexpiprazole in pregnancy and lactation, and because brexpiprazole is currently not recommended for use during pregnancy, the overall clinical and risk-benefit impact of this safety concern is unknown. Data obtained from participation in a Pregnancy Registry (refer to Part III.2) will be used to further characterize events of pregnancy with brexpiprazole.

Missing Information: Use in elderly (age > 65)	
Clinical and Risk-Benefit Impact	Typically, elderly patients are expected to have a worse safety profile with antipsychotics due to various co-morbidities and polypharmacy. In the schizophrenia indication, the elderly population was not systematically investigated. However, as in the MDD trial the elderly population and adults presented with a similar safety profile, it may be reasonable to expect similar outcomes for the schizophrenia indication.
Missing Information: Substance abuse, misuse, and overdose	
Clinical and Risk-Benefit Impact	Subjects who met DSM-IV-TR criteria for substance abuse or dependence within the previous 180 days; including alcohol and benzodiazepines (but excluding caffeine and nicotine) were excluded from the brexpiprazole clinical trial programme. No information is currently available for this subset of patients. In clinical trials and postmarketing experience on the accidental or intentional acute overdosage of brexpiprazole is currently limited. There was one record of an overdose (> 12 mg/day) of brexpiprazole in the schizophrenia trials (54 mg [27 2-mg tablets] taken by a subject in Trial 331-10-237). No TEAEs or other sequelae were reported as resulting from the overdose. Brexpiprazole exhibited a discriminative stimulus effect in rats. Brexpiprazole showed neither a reinforcing effect in rhesus monkeys nor a potential to induce physical dependence in rats. Thus, the drug abuse liability potential of brexpiprazole is considered to be very low. Although available preclinical data did not support potential for misuse for illegal purposes, atypical antipsychotic diversion, misuse and even dependency syndrome have been extensively reported in literature and may be considered a class effect. Data from the brexpiprazole clinical development program regarding misuse are limited. The overall clinical and risk-benefit impact of this safety concern is therefore unknown; however it is anticipated that this risk is low.
Missing Information: Use in patients with insulin-dependent diabetes mellitus (IDDM)	
Clinical and Risk-Benefit Impact	Unknown; IDDM is a frequent comorbidity in patients with schizophrenia, however subjects with IDDM were not studied in the brexpiprazole clinical trial programme. No information is currently available to determine the safety of brexpiprazole in patients with IDDM. The overall clinical and risk-benefit impact of this safety concern is therefore unknown. However, patients with stable Type II diabetes mellitus (DM) were included in the clinical trial programme, and no worsening in safety profile in this population was observed. Regular monitoring of blood glucose is recommended in the proposed SmPC in Section 4.4 (refer to Part V)

2.7.2 SVII.2: New Safety Concerns and Reclassification with a Submission of an Updated RMP

No safety concerns were identified or reclassified in this RMP.

2.7.3 SVII.3: Details of Important Identified Risks, Important Potential Risks, and Missing Information

2.7.3.1 SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks

Details of Important Identified Risks and Important Potential Risks

There are no important identified and no important potential risks for brexpiprazole.

2.7.3.2 SVII.3.2: Presentation of Missing Information

Details of Missing Information

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
MedDRA Terms	HLT: Exposures associated with pregnancy, delivery, and lactation
Evidence Source(s)	Clinical trials In clinical trials conducted with brexpiprazole, no pregnant or lactating women have been included. Pregnancy, or positive pregnancy test or breast-feeding was part of the exclusion criteria. Women who became pregnant during a clinical trial were withdrawn from the trial and treatment was discontinued. Safety database Cumulatively as of 09 Jul 2022, a total of 206 cases (111 spontaneous, 2 literature, 32 non-interventional and 61 interventional) including 365 AEs, of which 49 (13.4%) serious, were reported with use of brexpiprazole during pregnancy. Foetal outcome was reported in 56 out of 206 reports: normal 47/56 (83.9%), perinatal complication 6/56 (10.7%) and death 3/56 (5.4%). Similarly, birth type was reported in 55 out of 206 reports: full-term 23/55 (41.8%), elective termination 11/55 (20.0%), spontaneous abortion 11/55 (20.0%), premature 8/55 (14.5%), and outcome pending 2/55 (3.6%). The cumulative search of the safety database through 09 Jul 2022 using query PTs Exposure via breast milk, Intoxication by breast feeding, and Maternal exposure during breast feeding, identified a total of 12 cases (10 spontaneous, 2 literature) including 19 events, all non-serious. In 9 cases, no clinical AEs were reported, while the remaining 3 cases included the following AEs: febrile convulsion, overweight, drug ineffective, and nasal obstruction (each with one occurrence). Data from National Pregnancy Registry for Atypical Antipsychotics (NPRAA) Brexpiprazole use during pregnancy is monitored within the pregnancy registry based at the Center for Women's Mental Health at Massachusetts General Hospital in Boston, United States. There have been no cases of major malformations associated with use of brexpiprazole during the first trimester of pregnancy. There have been and continue to be subjects enrolled in the registry to date on brexpiprazole during pregnancy, but the number is not large enough for a separate publication. In the most recently published paper on data from the registry[120] brexpiprazole was included in the aggregate sample of 15 antipsychotic drugs. Data from the registry assessing second-generation antipsychotics as a class indicate that they are unlikely to have a major teratogenic effect. Pregnant and breastfeeding female patients remain a population in need of further characterisation.

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly (age > 65)**
MedDRA Terms	N/A

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly (age > 65)**
Evidence Source(s)	Clinical trials Although the elderly and adult population presented with a similar safety profile in a dedicated MDD trial, and it may be reasonable to expect similar outcomes for schizophrenia, the elderly population was not systematically investigated in the schizophrenia indication. Two phase 3 trials (Trial 331-12-283 and 331-12-284) were conducted in subjects with agitation associated with dementia of the Alzheimer's type (AAD). The objective of Trial 331-12-283 was to compare the safety and efficacy of 2 fixed doses (1 and 2 mg/day) of brexpiprazole with placebo in elderly subjects with AAD, and Trial 331-12-284 was conducted to evaluate the safety and efficacy of flexible dosing (0.5 to 2 mg/day) of brexpiprazole with placebo in elderly subjects with AAD. Safety results indicated that brexpiprazole was safe and well-tolerated in the elderly population. Currently, there are 4 ongoing clinical studies in subjects 65 years or older for indication of agitation associated with dementia of the Alzheimer's type and one study for indication of MDD. Safety database In the safety database, cumulatively as of 09 Jul 2022, a total of 1052 case reports (756 spontaneous, 139 non-interventional and 157 interventional) were identified for elderly population (age > 65). The cumulative number of AEs in elderly population comprised 6.05% of all the AEs reported for Brexpiprazole (2461/40673). The SOCs with the highest number of AEs reported included: Nervous system disorders (432; 17.5%), General disorders and administration site conditions (430; 17.5%), Injury, poisoning and procedural complications (426; 17.3%), and Psychiatric disorders (371; 15.1%). Of the total 2461 AEs, 532 (21.6%) were assessed as serious. Most common serious event PTs included Pneumonia (18/532; 3.4%), Fall (17/532; 3.2%), Neuroleptic malignant syndrome (15/532; 2.8%), Pneumonia aspiration (15/532; 2.8%), and Tardive dyskinesia (15/532; 2.8%). A total of 89 fatal events were reported during the cumulative period comprising 3.6% (89/2461) of the total AEs in elderly. Although the review and analysis of available safety information reported with the use of brexpiprazole does not provide evidence impacting the product benefit-risk balance among the elderly, the MAH has concluded that use in elderly remains a brexpiprazole core safety concern, until more data for this population become available. Elderly (age > 65) remains a population in need of further characterisation.

2.8 Module SVIII: Summary of the Safety Concerns

Important identified and potential risks and missing information for the brexpiprazole programme are listed in Table 2.8-1.

Table 2.8-1	**SVIII-1: Summary of Ongoing Safety Concerns**
Important Identified Risks	• None
Important Potential Risks	• None
Missing Information	• Use in pregnancy and lactation • Use in elderly (age > 65)

3 PART III: PHARMACOVIGILANCE PLAN (Including Postauthorisation Safety Studies)

3.1 III.1: Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

3.2 III.2: Additional Pharmacovigilance Activities

The MAH currently provides financial support to the pregnancy registry described below, based at the Center for Women's Mental Health at Massachusetts General Hospital in Boston, United States, and initiated by Dr. PPD , M.D and an academic group receiving financial support from a number of pharmaceutical companies.

The MAH proposes to continue utilising updates from this registry, as they are made available by the registry owners, to provide data on the use of brexpiprazole during pregnancy, which is currently considered Missing Information.

This Registry study is included as category 3 in Table 3.3-1, but the MAH notes that the study is an independent study not under the MAH's control.

The detailed protocol (Version Date: June 6, 2022) is included in Annex 3.
Study short name and title:

NPRAA: National Pregnancy Registry for Atypical Antipsychotics

Rationale and study objectives:

The NPRAA is the first hospital-based pregnancy registry for atypical antipsychotics in America designed to systematically and prospectively monitor pregnancy outcomes. Use in pregnancy is currently considered missing information for brexpiprazole.

Specific aims of the Registry are as follows:

Primary Aim: To prospectively evaluate rates of congenital malformations among infants exposed in utero to psychiatric medications.

Secondary Aims:

- To evaluate neonatal outcomes of infants with prenatal exposure to specific psychiatric medications alone or in combination with other psychotropics.
- To evaluate maternal health outcomes associated with use of psychiatric medication during pregnancy.

- To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to atypical antipsychotics.

Study design:

Prospective cohort; data on the reproductive safety of identified psychiatric medications will be collected prospectively through 3 telephone interviews.

Study population:

The intended study population includes pregnant women, age < 45, who are able to provide informed consent and willing to participate over the telephone. Women who have completed their pregnancy, are planning to become pregnant, or who are not taking any psychiatric medications and/or have no history of psychiatric illness will be excluded.

The target enrolment for this study is N=2500 women taking atypical antipsychotics, and N=2500 women who are not taking atypical antipsychotics but may be taking ADHD medications, antidepressants, sedative hypnotics or other psychiatric medications.

Milestones:
As the study is not owned by the MAH, data will be reviewed on an ongoing basis as it is provided to the MAH as per associated published literature, utilised in signal detection, and provided in the PBRER/PSUR, when available.

There are currently no further planned pharmacovigilance activities for brexpiprazole.

3.3 III.3: Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1 III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation - Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances - Not applicable				

Table 3.3-1 III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities				
Study and Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3- Required additional pharmacovigilance activities				
Data collection from participation in the Pregnancy Registry - NPRAA Ongoing	Primary: To prospectively evaluate rates of congenital malformations among infants exposed in utero to psychiatric medications Secondary: 1) To evaluate neonatal outcomes of infants with prenatal exposure to specific psychiatric medications alone or in combination with other psychotropics 2) To evaluate maternal health outcomes associated with use of psychiatric medication during pregnancy 3) To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to atypical antipsychotics	Missing Information: Use in pregnancy and lactation	Periodic updates	Data have been reviewed on an ongoing basis as it is provided to the MAH as per associated published literature, and utilised in signal detection and provided in the PBRER/ PSUR when available.

4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

There is no PAES planned or ongoing for brexpiprazole.

5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

5.1 V.1 Routine Risk Minimisation Measures

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern	
Safety Concern	**Routine Risk Minimisation Activities**
Use in pregnancy and lactation	Routine risk communication: • SmPC Sections 4.6, 5.3 • PL Section 2 Legal status: Prescription only medicine.
Use in elderly (age >65)	Routine risk communication: • SmPC Sections 4.2, 4.4, 5.2 • PL Section 2 Legal status: Prescription only medicine.

5.2 V.2: Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 V.3: Summary of Risk Minimisation Measures

Table 5.3-1 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in pregnancy and lactation	Routine risk minimisation measures: • SmPC Sections 4.6, 5.3 • PL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Data collection from participation in the NPRAA

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in elderly (age >65)	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, 5.2 • PL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 VI.1: Summary of the Risk Management Plan for RXULTI

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

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

This summary of the RMP for RXULTI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 RXULTI’s RMP.

6.1.1 I: The Medicine and What it is Used for

RXULTI is authorised for the treatment of schizophrenia in adults and adolescents aged 13 years and older (see SmPC for the full indication). It contains brexpiprazole as the active substance and it is given orally.

Further information about the evaluation of RXULTI’s benefits can be found in RXULTI’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/rxulti

6.1.2 II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of RXULTI together with measures to minimise such risks and the proposed studies for learning more about RXULTI'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.

If important information that may affect the safe use of RXULTI is not yet available, it is listed under `missing information' below.

6.1.2.1 II.A: A List of Important Risks and Missing Information

Important risks of RXULTI 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 RXULTI. 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).

Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information

Important Identified Risks	• None
Important Potential Risks	• None
Missing Information	• Use in pregnancy and lactation • Use in elderly (age > 65).

6.1.2.2 II.B: Summary of Important Risks and Missing Information

Table 6.1.2.2-1 II.B-1: Use in Pregnancy and Lactation	
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: • SmPC Sections 4.6, 5.3 • PL Section 2 Legal status: Prescription only medicine **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	Data collection from participation in the NPRAA

Table 6.1.2.2-2 II.B-2: Use in Elderly (> 65)	
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication: • SmPC Sections 4.2, 4.4 • PL Section 2 Legal status: Prescription only medicine **Additional risk minimisation measures:** No additional risk minimisation measures.

6.1.2.3 II.C: Post-authorisation Development Plan

6.1.2.3.1 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 RXULTI.

6.1.2.3.2 II.C.2 Other Studies in Post-authorisation Development Plan

NPRAA

Purpose of the study: To systematically and prospectively monitor pregnancy outcomes in individuals using atypical antipsychotics.

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7 PART VII: ANNEXES TO THE RISK MANAGEMENT PLAN

7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

7.6 Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.