SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

RXULTI 4 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RXULTI 4 mg film-coated tablets
Each film-coated tablet contains 4 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 42.2 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

RXULTI 4 mg film-coated tablets
White, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 4 one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RXULTI is indicated for the treatment of schizophrenia in adults and adolescents aged 13 years and older.

4.2 Posology and method of administration

Posology

Adult population
The recommended starting dose for brexpiprazole is 1 mg once daily on days 1 to 4.
Based on the patient's clinical response and tolerability, the brexpiprazole dose can be titrated to 2 mg once daily on day 5 through day 7 and then to 4 mg on day 8.
The recommended target dose range is 2 mg to 4 mg once daily. The maximum recommended daily dose is 4 mg.

Paediatric population
The recommended starting dose for brexpiprazole is 0.5 mg once daily on days 1 to 4.
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 dose is 4 mg.

Switching from other antipsychotics to brexpiprazole
When switching from other antipsychotics to brexpiprazole, gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while brexpiprazole treatment is initiated.

Switching to other antipsychotics from brexpiprazole
When switching to other antipsychotics from brexpiprazole, no gradual cross-titration is needed. The new antipsychotic should be initiated in its lowest dose while brexpiprazole is discontinued. It should be considered that plasma concentration of brexpiprazole will decline gradually and will be completely washed out in 1 to 2 weeks.

Special populations

Elderly
The safety and efficacy of brexpiprazole in the treatment of schizophrenia in patients aged 65 years and older have not been established (see sections 4.4 and 5.2). It is not possible to advise on a minimum effective/safe dose in this population.

Renal impairment
The maximum recommended dose in patients with moderate to severe impaired renal function is reduced to 3 mg once daily (see section 5.2).

Hepatic impairment
The maximum recommended dose in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) is reduced to 3 mg once daily (see section 5.2).

CYP2D6 poor metabolisers
Dosing modifications to half the recommended doses is required for patients with known CYP2D6 poor metaboliser status. Further dosing modifications to a quarter of the recommended dose is required for known CYP2D6 poor metabolisers while taking strong or moderate CYP3A4 inhibitors (see sections 4.5 and 5.2).

Dose adjustments due to interactions
Dose adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors/inducers or strong CYP2D6 inhibitors. If the CYP3A4 inhibitor/inducers or CYP2D6 inhibitor is withdrawn, the brexpiprazole dose may need to be returned to the dose used before the initiation of the concomitant therapy (see section 4.5). In case of adverse reactions despite dose adjustments of RXULTI, the necessity of concomitant use of RXULTI and CYP2D6 or CYP3A4 inhibitor should be reassessed.

Table 1: Dose adjustments of RXULTI in patients who are CYP2D6 poor metabolisers and for concomitant use with CYP inhibitors

Factors	**Adjusted dose**
CYP2D6 poor metabolisers	
Known CYP2D6 poor metabolisers	Administer half of the recommended dose

Factors	Adjusted dose
Known CYP2D6 poor metabolisers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dose
Patients taking CYP2D6 inhibitors and/or CYP3A4 inhibitors	
Strong CYP2D6 inhibitors	Administer half of the recommended dose
Strong CYP3A4 inhibitors	Administer half of the recommended dose
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dose

Patients taking strong CYP3A4 inducers
If brexpiprazole is used concomitantly with strong CYP3A4 inducers (e.g., rifampicin), in a patient stabilised on brexpiprazole it is necessary to titrate the daily dose of brexpiprazole stepwise up to double the recommended dose over the course of 1 to 2 weeks. Thereafter, if according to the clinical response, further dose adjustments are required, the dose may be increased up to a maximum of three times the recommended daily dose. Daily dose must not exceed 12 mg when brexpiprazole is used concomitantly with strong CYP3A4 inducers. Twice daily divided dosing of brexpiprazole is preferable, as once daily dosing results in high peak to trough fluctuation (see section 4.5).
CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Paediatric population
The safety and efficacy of brexpiprazole in children and adolescents aged less than 13 years have not been established. No data are available.

Method of administration

Oral use.
The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored throughout this period.

Suicidal ideation and behaviour
The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with brexpiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders
Brexpiprazole has not been evaluated in patients with a history of myocardial infarction/ischaemic heart disease or clinically significant cardiovascular disease since such patients were excluded from clinical trials.

Brexpiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension (including accelerated or malignant).

QT prolongation
QT prolongation can develop in patients treated with antipsychotics. In clinical trials, only a few, non-serious QT prolongations have been reported with brexpiprazole. Caution should be exercised when brexpiprazole is prescribed to patients with known cardiovascular disease, family history of QT prolongation, electrolyte imbalance or in case of concomitant use with other medicinal products thought to prolong the QT interval (see sections 4.8 and 5.1).

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotics. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with brexpiprazole, and preventive measures should be undertaken.

Orthostatic hypotension and syncope
Adverse reactions related to orthostatic hypotension can include dizziness, light-headedness and tachycardia. Generally, these risks are greatest at the beginning of treatment with antipsychotics and during dose escalation. Patients at increased risk of these adverse reactions (e.g., elderly) or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medicinal products, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, a lower starting dose and slower titration should be considered, and orthostatic vital signs should be monitored (see section 4.2).

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic treatment, including brexpiprazole (see section 4.8). Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include increased creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, brexpiprazole must be discontinued immediately.

Extrapyramidal symptoms (EPS)
Extrapyramidal symptoms (including acute dystonia) are known class effects for antipsychotics. Brexpiprazole should be used with caution in patients with a known history of EPS.

Tardive dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotics. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to

develop the syndrome. If signs and symptoms of tardive dyskinesia appear in a patient on brexpiprazole, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Cerebrovascular adverse reactions
In placebo-controlled trials with some antipsychotics in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects.

Elderly patients with dementia-related psychosis
Brexpiprazole has not been studied in elderly patients with dementia and is not recommended for the treatment of elderly patients with dementia due to increased risk of overall mortality.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes.
Patients treated with any antipsychotics, including brexpiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness). Fasting plasma glucose should be assessed before or soon after the initiation of the antipsychotic treatment. During long term treatment the plasma glucose levels should be monitored regularly for worsening of glucose control.

Weight gain and dyslipidaemia
Antipsychotics including brexpiprazole have been associated with metabolic changes, including weight gain and dyslipidaemia. An increased frequency of weight gain has been observed with increased duration of brexpiprazole treatment (see section 4.8). At the beginning of treatment, the lipid profile should be assessed. Clinical monitoring of weight and lipid profile is recommended at baseline and during treatment.

Seizures
As with other antipsychotics, brexpiprazole should be used with caution in patients who have a history of seizure disorder or other conditions that potentially lower the seizure threshold. Seizures have been reported during use of brexpiprazole (see section 4.8).

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised when prescribing brexpiprazole for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity, or being subject to dehydration.

Dysphagia
Oesophageal dysmotility and aspiration have been associated with antipsychotic use. Brexpiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Impulse-control disorders
Impulse-control disorders including gambling disorder have been reported in patients treated with brexpiprazole. Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking brexpiprazole. Other reported urges include compulsive sexual behaviours, compulsive shopping, binge eating, and other impulsive and compulsive behaviours. Patients with a prior history of impulse-control disorders may be at increased risk and should be monitored carefully. Because patients may not recognise these behaviours as abnormal, it is important for prescribers to ask patients or their caregivers

specifically about the development of new or increased impulse-control disorders or other compulsive behaviours while being treated with brexpiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced, or the medicinal product was discontinued. Compulsive behaviours may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medicinal product if a patient develops such urges while taking brexpiprazole (see section 4.8).

Leukopenia, neutropenia and agranulocytosis
Leukopenia, neutropenia and agranulocytosis (including fatal cases) have been reported during treatment with antipsychotics. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and brexpiprazole should be discontinued at the first sign of decline in WBC, in the absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 000/mm^3) should discontinue brexpiprazole and have their WBC followed until recovery.

Prolactin
Brexpiprazole can elevate prolactin levels. Elevations associated with brexpiprazole treatment are generally mild and may decline during administration, however, in some infrequent cases the effect may persist during administration (see section 4.8).

Lactose
RXULTI film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Brexpiprazole is predominantly metabolised by CYP3A4 and CYP2D6.

Potential for other medicinal products to affect brexpiprazole

CYP3A4 inhibitors
Co-administration of ketoconazole (200 mg twice daily for 7 days), a potent inhibitor of CYP3A4, with a 2 mg single oral dose of brexpiprazole increased the AUC of brexpiprazole by 97 % and did not change the C_{max}. Based on results of interaction studies, dose adjustment of brexpiprazole to half the dose is recommended when administered concomitantly with strong CYP3A4 inhibitors (itraconazole, ketoconazole, ritonavir, and clarithromycin).

CYP3A4 inducers
Co-administration of rifampicin (600 mg twice daily for 12 days), a potent CYP3A4 inducer, with a single 4 mg oral dose of brexpiprazole resulted in an approximate 31 % and 73 % decrease in brexpiprazole C_{max} and AUC, respectively. If brexpiprazole is used concomitantly with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, rifampicin, St. John’s Wort), the total daily dose

requirement of brexpiprazole is increased by approximately a factor of three times the recommended daily dose. Once daily dosing of brexpiprazole in case of co-administration with CYP3A4 inducers results in high peak to trough fluctuation (see section 4.2).

CYP2D6 inhibitors
Co-administration of a 2 mg single oral dose of brexpiprazole with quinidine (324 mg/day for 7 days), a potent inhibitor of CYP2D6, increased the AUC of brexpiprazole by 94 % and did not change the C_{max}. Based on results of interaction studies, dose adjustment of brexpiprazole to half the dose is recommended when administered concomitantly with strong CYP2D6 inhibitors (quinidine, paroxetine, and fluoxetine).

Based on estimations from the population pharmacokinetic analysis, CYP2D6 extensive metabolisers receiving both CYP3A4 and CYP2D6 inhibitors or CYP2D6 poor metabolisers receiving strong CYP3A4 inhibitors are expected to have approximately 4-fold to 5-fold increase in brexpiprazole concentrations and dose adjustment to a quarter of the dose is recommended for these subjects (see section 4.2).

Potential for brexpiprazole to affect other medicinal products

Based on results of *in vitro* studies, brexpiprazole is unlikely to cause clinically important pharmacokinetic interactions with medicinal products metabolised by cytochrome P450 enzymes. Brexpiprazole does not affect absorption of medicinal products that are substrates of Breast Cancer Resistance Protein transporter (BCRP) and P-glycoprotein (P-gp) transporter.

If brexpiprazole is administered concomitantly with medicinal products known to cause QT prolongation (e.g., moxifloxacin) or electrolyte imbalance (e.g., diuretics such as furosemide, bendroflumethiazide), caution should be used.

If brexpiprazole is administered concomitantly with medicinal products known to increase creatine phosphokinase (CPK), e.g., statins like simvastatin, the possible additive effect with CPK increase induced by brexpiprazole should be considered.

Pharmacodynamic interactions
No information on pharmacodynamic interactions of brexpiprazole is available at present. Caution should be exercised when prescribing other medicinal products concomitantly. Given the primary Central Nervous System (CNS) effects of brexpiprazole, caution should be used when brexpiprazole is taken in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as opiates like codeine or morphine (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of brexpiprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Brexpiprazole is not recommended during pregnancy and in women of childbearing potential not using contraception.

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.

Breast-feeding

It is unknown whether brexpiprazole/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of brexpiprazole/ metabolites in milk of rats (see section 5.3). A risk to the new-borns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from brexpiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of brexpiprazole on human fertility has not been evaluated. Studies in animals have shown decreased female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Brexpiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system effects, such as sedation and dizziness that are common adverse drug reactions (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) in adults were akathisia (5.6 %) and weight gain (3.9 %) and in adolescents they were nausea (6.4%), somnolence (4.5%) and akathisia (3.6%).

Tabulated list of adverse reactions

The incidences of the ADRs associated with brexpiprazole therapy are tabulated below. The table is based on adverse reactions reported in short-term placebo-controlled phase 2 and 3 adult clinical trials with relevant therapeutic doses (2 mg to 4 mg) and short-term placebo-controlled phase 3 paediatric clinical trials with relevant therapeutic doses (1 mg to 4 mg).

All ADRs are listed by system organ class (SOC) and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

SOC	Very common	Common	Uncommon	Not known
Immune system disorders		Rash	Angioedema Urticaria Swelling face	
Metabolism and nutrition disorders		Weight increase		
Psychiatric disorders			Suicide attempt Suicidal ideation	Gambling disorder Impulsive behaviour Binge eating Compulsive shopping Compulsive sexual behaviour
Nervous system disorders		Akathisia Dizziness Tremor Somnolence[1]	Parkinsonism	Seizures Neuroleptic malignant syndrome (NMS)
Cardiac disorders				Electrocardiogram QT prolonged
Vascular disorders			Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders			Cough	
Gastrointestinal disorders		Diarrhoea Nausea Abdominal pain upper	Dental caries Flatulence	
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity	Myalgia	Rhabdomyolysis
Pregnancy, puerperium and perinatal conditions				Drug withdrawal syndrome neonatal (see section 4.6)

SOC	Very common	Common	Uncommon	Not known
Investigations	Blood prolactin increased[2]	Blood creatine phosphokinase increased	Blood pressure increased Blood triglycerides increased Hepatic enzymes increased	

[1] Includes also sedation and hypersomnia

[2] The categorisation of blood prolactin increased is based on Potentially Clinically Relevant (PCR) criteria of > 1 × upper limit of normal (ULN).

Description of selected adverse reactions

Adults

Extrapyramidal Symptoms (EPS)

Akathisia was the most frequently reported EPS related ADR in the brexpiprazole 2 mg/day to 4 mg/day group (5.6 %) compared to 4.5 % in placebo, followed by tremor (2.7 %) compared to 1.2 % in placebo. The incidences of other EPS-related ADRs reported in short-term, controlled trials are dyskinesia (0.4 %), extrapyramidal disorder (1.8 %) and Parkinsonism (0.4 %). See section 4.4.

Akathisia

From fixed-dose trials there appears to be a dose-response relationship for akathisia in patients treated with brexpiprazole, with an increasing frequency with higher doses. The incidence of akathisia in the brexpiprazole 1 mg/day, 2 mg/day, and 4 mg/day groups was 3.0 %, 4.6 %, and 6.5 %, respectively, compared with 5.2 % of subjects in the placebo group. The incidence of akathisia in the short-term, controlled trials (5.4 %) was similar to the incidence in the long-term, open-label trials (5.7 %).

Suicidal behaviour

In short-term, controlled trials, Treatment Emergent Adverse Events (TEAEs) related to suicidal behaviour were reported for 8 subjects (0.5 %, 2 serious events, 1 leading to discontinuation) in the brexpiprazole treatment group and 3 subjects (0.4 %, none-serious) in the placebo group. In long-term, open-label trials, TEAEs related to suicidal behaviour were reported for 23 subjects (1.6 %). Overall, in the brexpiprazole clinical development program for schizophrenia, one death due to suicide occurred but was not considered drug related by the investigator. Spontaneous cases reporting completed suicide and suicide attempt have been reported in the post-marketing setting. See section 4.4.

QT prolongation

In the short-term controlled trials with brexpiprazole, 3 TEAEs related to QT prolongation were reported in the 2 mg to 4 mg group (0.3 %), compared with 3 TEAEs (0.5 %) reported in subjects receiving placebo. The incidence of TEAEs in long-term trials was similar to that of the short-term trials.

The effects of brexpiprazole at therapeutic (4 mg) and supra-therapeutic (12 mg) doses on QT interval were evaluated in subjects with schizophrenia or schizoaffective disorder in a randomised, double-blind, placebo- and positive-controlled (moxifloxacin), parallel-arm trial. Subgroup analyses from this trial suggested that the QTc prolongation was larger in female subjects than in males (see sections 4.4, 4.5 and 5.1).

Weight gain

In short-term, controlled trials, the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % from baseline in body weight) was 9.1 % in the brexpiprazole 2 mg/day to 4 mg/day group, compared with 3.8 % in the placebo group.

In the long-term, open-label trial, the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % in body weight) at any visit was 20.7 % and 0.4 % of the subjects discontinued due to weight gain. In subjects who had a weight gain ≥ 7 % from baseline, weight increased over time, with mean weight gain up to 10.2 kg at week 52. The mean change in body weight overall for the brexpiprazole group in the long term, open label trial was 2.1 kg at week 52. See section 4.4.

Prolactin
The incidence of blood prolactin increased was 0.9 % in the 2 mg to 4 mg brexpiprazole group compared to 0.5 % in the placebo group in short-term, controlled trials. Higher frequencies of prolactin increased (1.5 % *versus* 0.60 %) were observed in females compared to males in short-term trials. In addition, the frequencies of prolactin elevations > 1 × ULN in the 2 mg to 4 mg brexpiprazole group was 13.7 % in females *versus* 6.4 % in the placebo group and 11.1 % in males *versus* 10.3 % in the placebo group. See section 4.4.

Neuroleptic malignant syndrome
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with brexpiprazole (see section 4.4).

Nausea
For nausea, the incidence in the 2 mg to 4 mg brexpiprazole group was 2.3 % overall in short-term controlled trials, compared to 2.0 % in the placebo group. For vomiting, these incidences were 1.0 % in the brexpiprazole-treated group compared to 1.2 % in the placebo group.

In terms of gender differences, there were higher observed frequencies of nausea (4.8 % *versus* 2.8 %) and vomiting (4.6 % *versus* 1.4 %) in females compared to males among brexpiprazole-treated subjects in short-term trials. Concerning subjects receiving placebo, the frequency for nausea was 2.8 % for males *versus* 3.2 % for females, whereas the frequency for vomiting was 3.0 % for males *versus* 2.6 % for females (see section 5.2).

Paediatric population

Adolescents aged 13 years and older with schizophrenia
Frequency, type and severity of adverse reactions in adolescents are expected to be similar as in adults.

Extrapyramidal Symptoms (EPS)
In short-term trials, akathisia was the most frequently reported EPS related ADR in the brexpiprazole 1 mg/day to 4 mg/day group (3.6 %) compared to 2.9 % in placebo. The incidences of other EPS-related ADRs reported in short-term, controlled trials in paediatric patients were muscle rigidity (0.9 %), hypokinesia (0.9 %) and tremor (0.9 %).

Akathisia
The incidence of akathisia in the brexpiprazole-treated paediatric subjects in a short-term, randomized, double-blind trial was 3.6 % versus 2.9 % for placebo-treated subjects. The incidence of akathisia in the ongoing-long-term, open label trial was 5.1 %. See section 4.4.

Suicidal behaviour
In a short-term, controlled trial, a TEAE of suicidal behaviour was reported in 1 subject (0.9 %, non-serious event) in the brexpiprazole treatment group and none in the placebo group. In a long-term, open-label trial, TEAEs of suicidal behaviour were reported in 8 subjects (2.7 %). See section 4.4.

QT prolongation

No TEAEs related to QT prolongation have been reported in the adolescent schizophrenia trials. The safety profile observed in the adolescent population is considered to be similar to that observed in the adult population (see section 4.4).

Weight gain
In a short-term, controlled trial the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % from baseline in body weight) was 8.2 % in brexpiprazole treated group, compared with 4.9 % in placebo group The mean increase in weight from baseline to last visit was 0.8 kg in brexpiprazole and 0.0 kg in placebo-treated subjects. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for natural growth of children and adolescents by comparisons to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this study, no change in mean z-score from baseline to last visit was observed in brexpiprazole and placebo-treated groups. 4.5 % of subjects in brexpiprazole and 3.9 % subjects in placebo had an increase in age-and-gender-adjusted body weight z-score of at least 0.5 SD from baseline. TEAEs of weight gain was reported in 1.7% of all patients in the brexpiprazole group compared to 3.4% in placebo group. See section 4.4.

In the long-term, open-label trial, the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % from baseline in body weight) at any visit was 44.6% in brexpiprazole treated group. Mean change in z-score from baseline to last visit was 0.10 SD for body weight, while 20% of patients had an increase in age-and gender-adjusted body weight z-score of at least 0.5 SD from baseline. TEAEs related to weight increased were observed in 11.5 % of subjects, while other TEAEs related to weight increase, such as increased BMI and waist circumference, were each reported in one subject.

Prolactin
In the short-term trial, no treatment emergent adverse events associated with elevated prolactin were reported. The frequencies of prolactin elevations > 1 × ULN in the 2 mg to 4 mg brexpiprazole group was 26.8 % in females *versus* 6.3 % in the placebo group and 24.5 % in males *versus* 6 % in the placebo group. In the long-term trials, 1.7% of the subjects reported TEAEs of blood prolactin increased and 0.7% subjects reported TEAEs of hyperprolactinaemia. See section 4.4.

Neuroleptic malignant syndrome
No TEAEs related to NMS have been reported in the adolescent schizophrenia trials. The safety profile observed in the adolescent population is considered to be similar to that observed in the adult population (see section 4.4).

Nausea
TEAEs of Nausea have been reported in the adolescent schizophrenia trials. The safety profile observed in the adolescent population is considered to be similar to that observed in the adult population.

Somnolence including sedation and hypersomnia
In short-term trials, the incidence of somnolence-related TEAEs (sedation, somnolence, hypersomnia) was 7.3% in the brexpiprazole 2-4 mg group compared to 6.7% in the placebo group. In a long-term, open-label trial, the incidence of somnolence-related TEAEs (sedation, somnolence, hypersomnia) was 11.9%. These TEAEs were mild to moderate in severity.

Reporting of suspected adverse reactions

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

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

4.9 Overdose

Gastric lavage and treatment with an emetic may be useful immediately after overdose. An electrocardiogram should be obtained in case of overdose and if QT interval prolongation is present, cardiac monitoring should be instituted.

Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting 2 mg oral dose of brexpiprazole, decreased brexpiprazole C_{max} and AUC by approximately 5 % to 23 % and 31 % to 39 % respectively. However, there is insufficient information available on the therapeutic potential of activated charcoal in treating an overdose with brexpiprazole.

Although there is no information on the effect of haemodialysis in treating an overdose with brexpiprazole, haemodialysis is unlikely to be useful in overdose management since brexpiprazole is highly bound to plasma proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code N05AX16

Mechanism of action

Brexpiprazole is an atypical antipsychotic agent. The pharmacology of brexpiprazole is believed to be mediated by a modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (Ki: 0.1 nM to 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ receptors with affinity in the same sub-nanomolar Ki range (Ki: 0.2 nM to 0.6 nM).

Pharmacodynamic effects

Influences of genetic variation on the pharmacodynamic responses to brexpiprazole have not been investigated.

Effects on QT
The effects of brexpiprazole on the QT interval were evaluated in patients with schizophrenia or schizoaffective disorder. In the overall analysis, brexpiprazole did not prolong the QT_c interval to a clinically relevant extent following therapeutic and supra-therapeutic doses

(4 mg/day; n = 62 or 12 mg/day; n = 53) and no correlation has been observed between brexpiprazole concentrations and QT_c prolongation.

Subgroup analyses from the thorough QT_c trial suggested that the QT_c prolongation was larger in female subjects than in males. In the brexpiprazole 4 mg/day group, the maximum placebo-adjusted mean change from baseline in the QT_{cI} interval was 5.2 ms (90 % CI: 1.5, 8.9) in males (n = 48) and 15.0 ms (90 % CI: 7.7., 22.3) in females (n = 14) at 6 hours post-dosing. In the brexpiprazole 12 mg/day group, the maximum placebo-adjusted mean change from baseline in the QT_{cI} interval was 2.9 ms (90 % CI: −1.2, 6.9) in males (n = 40) at 12 hours post-dosing and 10.4 ms (90 % CI: 2.7, 18.2) in females (n = 13) at 24 hours post-dosing. The smaller number of female than male subjects enrolled in the study does not allow to draw definitive conclusions.

Clinical efficacy

Adults:
The efficacy and safety of brexpiprazole in the treatment of adults with schizophrenia was studied in two multi-national and one regional (Japan), 6-week, randomised, double-blind, placebo-controlled, fixed-dose clinical trials (trials 1 to 3), a multi-national, 6-week, randomised, double-blind, placebo-controlled, active reference (quetiapine), flexible-dose clinical trial (trial 4), and, one multi-national, placebo-controlled, 52-week maintenance trial (trial 5). The trials included 2690 patients with the age of 18 years to 65 years.

In trials 1, 2 and 3, brexpiprazole was titrated as described in section 4.2 with 1 mg for 4 days, followed by 2 mg on days 5 to 7. On day 8, the dose was increased to 4 mg for some of the treatment arms.

Short-term trials
In the three fixed-dose, short-term trials (trials 1, 2 and 3), subjects were randomised to brexpiprazole 2 mg once daily, 4 mg once daily or placebo.

Trial 4 assessed the efficacy, safety, and tolerability of brexpiprazole in a flexible dose range of 2 mg/day to 4 mg/day and 400 mg to 800 mg quetiapine extended release (XR) for assay sensitivity. In the short-term trials, the primary efficacy endpoint was defined as the mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total scores, a multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression.

The key secondary endpoint in trials 1, 2 and 4 was the Clinical Global Impression of Severity (CGI-S) of schizophrenia, a 7-point clinician's assessment of the severity of disease. The CGI-S was also assessed in trials 3 and 5 as secondary endpoint.

The effects of brexpiprazole were also evaluated across a number of pre-specified secondary endpoints: the specific aspects of symptoms of schizophrenia (PANSS Positive Subscale score, PANSS Negative Subscale score, PANSS Excited Component [PEC] score, PANSS Marder factors positive, negative, disorganised thoughts, uncontrolled hostility/excitement and anxiety/depression), and analyses of response (defined as 30 % improvement in PANSS total score compared to baseline or a CGI-I score of 1 [very much improved] or 2 [much improved]).

Efficacy was demonstrated in trial 1 for both brexpiprazole 2 mg/day and 4 mg/day and replicated in trial 2 only for brexpiprazole 4 mg/day and in trial 3 only for brexpiprazole 2 mg/day.

In the flexible-dose trial 4, at week 6, subjects in the brexpiprazole treatment group had numerically greater improvements on PANSS total score than the subjects in the placebo group, although, the difference at week 6 did not reach statistical significance for the primary efficacy analysis (p = 0.0560; see table 2). In the same trial, the active reference, quetiapine XR added for assay sensitivity only, separated from placebo.

Table 2: Primary efficacy results for 6-week trials in schizophrenia

Trial	Treatment group	n	Primary efficacy measure: PANSS			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a, b] (95 % CI)	p-value
1	Brexpiprazole (2 mg/day)*	180	95.85 (13.75)	−20.73 (1.55)	−8.72 (−13.1, −4.37)	< 0.0001
	Brexpiprazole (4 mg/day)*	178	94.70 (12.06)	−19.65 (1.54)	−7.64 (−12.0, −3.30)	0.0006
	Placebo	178	95.69 (11.46)	−12.01 (1.60)	--	--
2	Brexpiprazole (2 mg/day)	179	96.30 (12.91)	−16.61 (1.49)	−3.08 (−7.23, 1.07)	0.1448
	Brexpiprazole (4 mg/day)*	181	94.99 (12.38)	−20.00 (1.48)	−6.47 (−10.6, −2.35)	0.0022
	Placebo	180	94.63 (12.84)	−13.53 (1.52)	--	--
3	Brexpiprazole (2 mg/day)*	113	96.55 (19.20)	−14.95 (2.00)	−7.32 (−13.04, −1.59)	0.0124
	Brexpiprazole (4 mg/day)	109	96.39 (15.73)	−11.49 (2.10)	−3.86 (−9.71, 2.00)	0.1959
	Placebo	113	97.19 (19.27)	−7.63 (2.11)	--	--
4	Brexpiprazole (2 mg/day to 4 mg/day)	150	97.82 (10.25)	−19.99 (1.51)	−4.1 (−8.2, 0.1)	0.0560
	Placebo	159	98.38 (10.30)	−15.93 (1.49)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean.
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b The LS Mean, 95 % CI, and p-values for individual trials were derived from an MMRM (Mixed effect Model Repeat Measurement) analysis as follows: fixed effects of site, treatment, visit, and treatment-by-visit interaction, with baseline and baseline-by-visit interaction as covariates. Unstructured variance-covariance matrix structure was used.

The primary statistical analysis was performed using an MMRM model with MAR (Missing At Random) imputation. Results of a sensitivity analysis using placebo based multiple imputation (PMI) were consistent with the primary analysis.

Results for the (key) secondary outcome parameter and additional endpoints were supportive of the primary endpoint.

In trial 1, statistically significant greater improvement on the CGI-S, the key secondary efficacy measure, at week 6 was also shown for the 2 mg/day and 4 mg/day compared to the placebo dose groups. Due to the testing hierarchy the greater improvement shown for both 2 mg/day and 4 mg/day on the CGI-S can only be considered supportive for trials 2, 3 and 4 (see table 3).

Table 3: Key secondary efficacy results for 6-week trials in schizophrenia

Trial	Treatment group	n	Key secondary efficacy measure: CGI-S			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a] (95 % CI)	p-value
1	Brexpiprazole (2 mg/day)*	181	4.90 (0.64)	−1.15 (0.08)	−0.33 (−0.56, −0.10)	0.0056
	Brexpiprazole (4 mg/day)*	178	4.81 (0.64)	−1.20 (0.08)	−0.38 (−0.61, −0.15)	0.0012
	Placebo	181	4.84 (0.66)	−0.82 (0.09)	--	--
2	Brexpiprazole (2 mg/day)	180	4.96 (0.65)	−0.99 (0.09)	−0.19 (−0.42, 0.05)	0.1269
	Brexpiprazole (4 mg/day)*	183	4.85 (0.64)	−1.19 (0.08)	−0.38 (−0.62, −0.15)	0.0015
	Placebo	181	4.87 (0.61)	−0.81 (0.09)	--	--
3	Brexpiprazole (2 mg/day)*	113	4.80 (0.78)	−0.84 (0.11)	−0.35 (−0.67, −0.03)	0.0308
	Brexpiprazole (4 mg/day)	109	4.71 (0.75)	−0.64 (0.12)	−0.16 (−0.48, 0.17)	0.3461
	Placebo	113	4.73 (0.71)	−0.48 (0.12)	--	--
4	Brexpiprazole* (2 mg/day to 4 mg/day)[b]	150	4.96 (0.59)	−1.21 (0.08)	−0.27 (−0.49, −0.06)	0.0142
	Placebo	159	4.94 (0.57)	−0.93 (0.08)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b Mean dose 3.5 mg/day

Maintenance of efficacy trial

In trial 5, a long-term trial designed to assess the maintenance of effect of brexpiprazole by assessing the delay in time to impending relapse of schizophrenia, patients with schizophrenia, who responded to treatment with brexpiprazole 1 mg/day to 4 mg/day, were stabilised over 12 weeks to 36 weeks, and then randomised in a double-blind manner to either

continue treatment with the stabilisation dose of brexpiprazole (n = 96) or to receive placebo (n = 104) for 52 weeks or until relapse occurred.

In the primary analysis of time to impending relapse patients on brexpiprazole showed a significantly longer time to relapse compared with patients on placebo ($p < 0.0001$). At week 52 brexpiprazole (13.5 %) reduced the risk of impending relapse by 71 % compared with placebo (38.5 %). During the stabilisation, brexpiprazole improved clinical symptomology (as assessed by PANSS, CGI-S and CGI-I, [Analysis of Covariance - ANCOVA Last Observation Carried Forward - LOCF]) and functioning (as assessed by Global Assessment of Functioning (GAF) [ANCOVA LOCF]). These improvements were maintained during the 52-week double-blind maintenance phase in patients on brexpiprazole whereas patients randomised to placebo showed deterioration in PANSS, CGI-S and CGI-I, and GAF scores [ANCOVA LOCF]). Brexpiprazole maintained symptom control and functioning compared to placebo.

Paediatric population
The efficacy and safety of brexpiprazole in the treatment of paediatric patients with schizophrenia was studied in one 6-week, randomised, double-blind and placebo- controlled trial (trial 6) and an on-going long-term, 24-month open-label trial. The short-term trial included 110 patients randomized to brexpiprazole, 101 patients to aripiprazole for assay sensitivity and 104 patients to placebo with a mean age of 15 years.
In the short-term trial (trial 6), patients received either brexpiprazole 2 to 4 mg/day, aripiprazole 10 to 20 mg/day or placebo.

The primary efficacy endpoint was defined as the mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total scores.

Brexpiprazole 2 to 4 mg/day and aripiprazole showed statistically significant improvements compared to placebo in the mean change from baseline in the PANSS Total Score.

Interim analyses from long-term trial with flexible doses of brexpiprazole 1 to 4 mg/day showed maintained improvement in symptoms from baseline through month 24 in PANSS Total Score.

Table 4: Primary efficacy results for 6-week trial in schizophrenia in Paediatric Patients

Trial	**Treatment group**	**n**	**Primary efficacy measure: PANSS**			
			Mean baseline score (SD)	**LS mean change from baseline (SE)**	**LS mean difference[a] (95 % CI)**	**p-value**
6	Brexpiprazole (2 mg/day to 4 mg/day)*	110	101.06 (14.87)	-22.75 (1.49)	-5.33 (-9.55, -1.10)	0.0136
	Aripiprazole (10 mg/day to 20 mg/day)	101	101.03 (13.08)	-23.95 (1.57)	-6.53 (-10.8, -2.21)	0.0032
	Placebo	103[b]	102.17 (16.30)	-17.42 (1.58)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6

b Efficacy sample includes treated subjects who have baseline and at least 1 post-baseline efficacy evaluation for the PANSS Total Score

Furthermore, a pharmacokinetic/pharmacodynamic analysis has been considered supportive for the comparison of clinical efficacy data between adolescents and adults with schizophrenia.

5.2 Pharmacokinetic properties

Absorption

Brexpiprazole is absorbed after administration of the tablet, with peak plasma concentrations occurring within 4.0 hours after single dose administrations; the absolute oral bioavailability of the tablet formulation is 95.1 %. Brexpiprazole steady-state concentrations are attained within 10 days to 12 days of dosing. Administration of a 4 mg brexpiprazole tablet with a standard high fat meal did not significantly affect the C_{max} or AUC of brexpiprazole. After single and multiple once daily dose administration, brexpiprazole exposure (C_{max} and AUC) increase in proportion to the dose administered. Based on *in vivo* studies, brexpiprazole is neither a substrate nor an inhibitor of efflux transporters, such as Multi Drug Resistance (MDR) 1 (P-gp) and BCRP.

Distribution

The volume of distribution of brexpiprazole following intravenous administration is high (1.56 L/kg ± 0.418 L/kg), indicating extravascular distribution. Brexpiprazole is highly protein bound in plasma (greater than 99 %) to serum albumin and α1-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment. Based on results of *in vitro* studies brexpiprazole protein binding is not affected by warfarin, diazepam, and digitoxin.

Biotransformation

Based on *in-vitro* metabolism studies using recombinant human cytochrome P450, the metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites. Based on *in vitro* data brexpiprazole showed little to no inhibition of other CYP450 isozymes. *In-vivo*, the metabolism of brexpiprazole is mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites with only one metabolite, DM-3411, present in plasma with more than 10 % of plasma exposure.

At steady-state, DM-3411 represents 23.1 % to 47.7 % of brexpiprazole exposure (AUC) in plasma. It should be noted that *in-vivo* preclinical studies have shown that at clinically relevant plasma exposures of brexpiprazole, DM-3411 brain exposures were below the detection limit. Thus, DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

Elimination

Following a single oral dose of [^{14}C]-labelled brexpiprazole, approximately 24.6 % and 46 % of the administered radioactivity was recovered in the urine and faeces, respectively. Less than 1 % of unchanged brexpiprazole was excreted in the urine and approximately 14 % of the oral dose was recovered unchanged in the faeces. Apparent oral clearance of brexpiprazole tablet after once daily administration is 19.8 (± 11.4) mL/h/kg. After multiple

once daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.

Linearity/non-linearity

The pharmacokinetic of brexpiprazole is dose proportional and time-invariant after single-dose (0.2 mg to 8 mg) and multiple-dose (0.5 mg to 4 mg) using once-daily administration.

Pharmacokinetics in special populations

Age
After single dose administration of brexpiprazole (2 mg), elderly subjects (older than 65 years) exhibited similar brexpiprazole systemic exposure (C_{max} and AUC) in comparison with the adult subjects (18 years to 45 years old; see sections 4.2 and 4.4).

Gender
Population PK evaluation identified gender as statistically significant covariate. The exposure (AUC) of brexpiprazole in women was estimated to be 25 % higher than in men (see section 4.8).

Race
Although no specific pharmacokinetic study was conducted, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of brexpiprazole.

CYP2D6 genotype
Population pharmacokinetic evaluation shows that CYP2D6 poor metabolisers have 47 % higher exposure to brexpiprazole compared to extensive metabolisers (see section 4.2).

Smoking
Based on studies utilising human liver enzymes *in vitro*, brexpiprazole is not a substrate for CYP1A2. Therefore, smoking should not have an effect on the pharmacokinetics of brexpiprazole.

Renal impairment
In subjects (n = 10) with severe renal impairment (CL_{cr} < 30 mL/min), AUC of oral brexpiprazole (3 mg single dose) compared to matched healthy subjects was increased by 68 % while its C_{max} was not changed. For patients with moderate to severe renal impairment (creatinine clearance CL_{cr} < 60 mL/minute), the maximum recommended dose is reduced to 3 mg once daily (see section 4.2).

Hepatic impairment
In subjects (n = 22) with varying degrees of hepatic impairment (Child-Pugh Classes A, B, and C), the AUC of oral brexpiprazole (2 mg single dose), compared to matched healthy subjects, increased 24 % in mild hepatic impairment, increased 60 % in moderate hepatic impairment, and did not change in severe hepatic impairment. For patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C), the maximum recommended dose is reduced to 3 mg once daily (see section 4.2).

Paediatric population
A multiple dose PK study (0.5, 1, 2, 3 or 4 mg/day) has been conducted in 24 paediatric patients aged 13 years to 17 years old. Population PK analysis indicated systemic exposure (C_{max} and AUC) of brexpiprazole in paediatric patients (13 to 17 years of age) was comparable to that in adult patients across the dose range from 0.5 to 4 mg.

5.3 Preclinical safety data

Effects observed in repeated-dose toxicity studies in rats and monkeys were mainly related to the exaggerated pharmacological activity of brexpiprazole. No safety margins based on $AUC_{0\text{-}24\,h}$ at the Maximum Recommended Human Dose (MRHD) of 4 mg/day could be derived in both female and male rats and monkey.

Cardiovascular toxicity

Following oral administration, brexpiprazole decreased blood pressure and prolonged QT interval in safety pharmacology study in conscious male dog, in repeated-dose toxicity studies in male and female monkeys and in juvenile toxicity study in male and female dogs. The effect of brexpiprazole on blood pressure reduction is attributed to the expected blockade of α1-adrenoceptors in peripheral blood vessels.

Genotoxicity, carcinogenicity

Brexpiprazole did not show any genotoxic potential in both *in vitro* and *in vivo* studies using clinically relevant exposures. Brexpiprazole administered orally did not increase the incidence of tumours in a 2-year carcinogenicity study in both male and female rats and in male mice at exposures up to 4.4-fold and 3.1-fold the MRHD. In female mice, an increased incidence of mammary gland adenocarcinoma and adeno-squamous carcinoma, and pars distalis adenoma of the pituitary gland, was observed at similar or even lower clinically relevant exposures: these prolactin-mediated endocrine tumours were also observed in rodents with other antipsychotics and their clinical relevance is unknown.

Reproductive toxicity

Following oral administration, brexpiprazole did not affect male fertility in rats but prolonged diestrus and decreased fertility in female rats at similar or even lower exposure levels than those clinically achieved at MRHD. Significant increased pre-implantation losses were observed at 4.1-fold the clinical exposure at MRHD. In embryo-foetal developmental toxicity studies, brexpiprazole was not teratogen in orally treated rats up to exposure levels (based on data in non-pregnant rats) clinically achieved at MRHD. In rabbit, vertebral malformations were seen in 3 foetuses from 2 litters at maternally toxic brexpiprazole oral doses corresponding to exposure approximately 16.5-fold the clinical exposure at MRHD.

Delayed growth, physical development and impaired viability of the offspring were observed at maternally toxic brexpiprazole doses in a pre-/post-natal developmental toxicity study in orally administered rats.

Following oral administration in pregnant rats, foetus and milk transfer of brexpiprazole was demonstrated at concentrations that were generally comparable to levels seen in maternal blood.

Environmental risk assessment (ERA)

Brexpiprazole is very persistent and very bio-accumulative but not toxic, to the environment: possible enrichment of brexpiprazole in terrestrial food chains might pose a concern (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Low-substituted hydroxypropylcellulose
Hydroxypropylcellulose
Magnesium stearate
Purified water

Tablet coat

Hypromellose (E 464)
Talc (E 553b)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

RXULTI 0.25 mg, 0.5 mg, 2 mg, 3 mg and 4 mg film-coated tablets
28 film-coated tablets in Aluminium/PVC blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

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