AUSTRALIAN PRODUCT INFORMATION – REXULTI (BREXPIPRAZOLE) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Brexpiprazole.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

REXULTI contains brexpiprazole, a novel atypical antipsychotic agent. REXULTI is available as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets for oral use.

REXULTI tablets also contain the following inactive ingredients: lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose and magnesium stearate. The following OPADRY complete coating systems are also contained in the tablets: 0.25 mg tablets - 03A465005 BROWN (ARPING No 110573); 0.5 mg tablets - 03A430000 ORANGE (ARPING No 110574); 1 mg tablets - 03A420002 YELLOW (ARPING No 110572); 2 mg tablets - 03A410000 GREEN (ARPING No 110570); 3 mg tablets - 03A400000 PURPLE (ARPING No 110575) and 4 mg tablets - 03A480004 WHITE (ARPING No 110571).

3 PHARMACEUTICAL FORM

REXULTI® (brexpiprazole) tablets are available as:

Strength	Shape	Colour	Marking
0.25 mg*	Round, shallow convex and bevel-edged	light brown	debossed with BRX and 0.25 on one side
0.5 mg*	Round, shallow convex and bevel-edged	light orange	debossed with BRX and 0.5 on one side
1 mg	Round, shallow convex and bevel-edged	light yellow	debossed with BRX and 1 on one side
2 mg	Round, shallow convex and bevel-edged	light green	debossed with BRX and 2 on one side
3 mg	Round, shallow convex and bevel-edged	light purple	debossed with BRX and 3 on one side
4 mg	Round, shallow convex and bevel-edged	white	debossed with BRX and 4 on one side

*** Not currently marketed**

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

REXULTI is indicated in adult patients for the treatment of schizophrenia.

4.2 Dose and method of administration

The recommended starting dose for REXULTI in the treatment of patients with schizophrenia is 1 mg once daily on Days 1 to 4.

The recommended target dose range is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

Maintenance treatment: The recommended maintenance dose range is 2 mg/day to 4 mg/day. Periodically reassess to determine the continued need for maintenance treatment and appropriate dosage.

REXULTI can be given with or without food.

Use in Elderly

Similar exposure to brexpiprazole was seen when REXULTI was administered in healthy elderly subjects (older than 65 years) and in adult subjects (18-45 years old). (See Section 5.2 Pharmacokinetic properties) In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and other drug therapy.

Dosing Adjustment for Hepatic Impairment

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.

Dosing Adjustment for Renal Impairment

For patients with moderate, severe or end-stage renal impairment (creatinine clearance CL_{cr} <60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

Other Special Populations

No dosage adjustment for REXULTI is required on the basis of a patient's sex, race, or smoking status. (See Section 5.2 Pharmacokinetic properties)

Dosing Modifications for CYP2D6 Poor Metabolisers and for Concomitant Use with CYP Inhibitors/Inducers

Factors	Adjusted dose
CYP2D6 Poor Metabolisers	
Known CYP2D6 poor metabolisers	Administer half of the usual dose
Known CYP2D6 poor metabolisers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors	
Strong CYP2D6 inhibitors	Administer half of the usual dose
Strong CYP3A4 inhibitors	
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers*	Double usual dose over 1 to 2 weeks

* **If the co-administered CYP3A4 inducer is discontinued, reduce the dosage to the original level over 1 to 2 weeks**.

Abuse potential

Brexpiprazole showed neither a potential to produce physical dependence in rats nor a reinforcing effect in rhesus monkeys. In a drug abuse liability study in rats, no withdrawal signs suggestive of physical dependence were evident. Brexpiprazole is not considered to have potential to produce physical dependence.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Increased Mortality in Elderly Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo.

Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. REXULTI is not approved for the treatment of dementia-related psychosis.

Cerebrovascular Adverse Reactions

In placebo-controlled trials with some antipsychotic drugs 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.

Suicidal Risk

The possibility of a suicide attempt is inherent in psychotic illnesses. Close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. 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 REXULTI and preventive measures undertaken.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs including REXULTI. 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 elevated 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, all antipsychotic drugs including REXULTI must be discontinued. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. 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 REXULTI, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Metabolic Parameters

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.

Patients treated with any antipsychotic agents should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) should be monitored regularly for worsening of glucose control. In patients with significant treatment-emergent hyperglycaemia, discontinuation of REXULTI should be considered.

In clinical trials with REXULTI in patients with schizophrenia (Trials 1 and 2) changes in fasting glucose were comparable between REXULTI- and placebo-treated subjects.

In the long-term maintenance trial (Trial 3), the mean changes from baseline to last visit in serum glucose were also small for the REXULTI (2.11 mg/dL) and placebo (−1.62 mg/dL) groups, and not considered clinically relevant.

In the long-term, open-label studies, the mean change from baseline to last visit in fasting serum glucose was 2.31 mg/dL (N=1120).

Weight Gain and Dyslipidaemia

Antipsychotic drugs have been associated with metabolic changes, including weight gain and dyslipidaemia. Clinical monitoring of body weight is recommended. (See Section 4.8 Adverse Effects – Weight Gain and Section 4.8 Adverse Effects – Dyslipidaemia).

Orthostatic Hypotension and Syncope

In the short-term, placebo-controlled clinical studies of REXULTI in subjects with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in REXULTI-treated subjects compared to placebo-treated subjects included: dizziness (2.3% versus 1.4%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).

Adverse reactions related to orthostatic hypotension can include dizziness, light-headedness and tachycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, 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, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

QT interval

In a thorough QTc study in patients with schizophrenia or schizoaffective disorder, REXULTI did not prolong QT interval (see also Section 5.1 Pharmacodynamic properties). However, in patients with a family history of QT prolongation antipsychotics should be used with caution.

Seizures

As with other antipsychotic drugs, REXULTI should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing REXULTI 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 medication with anticholinergic activity, or being subject to dehydration.

Dysphagia
Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. REXULTI and other antipsychotic drugs should be used cautiously in patients at risk of aspiration pneumonia.

Leukopenia, Neutropenia and Agranulocytosis
Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

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 REXULTI 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 < 1000/mm^3) should discontinue REXULTI and have their WBC followed until recovery.

Impulse Control Disorders
Post-marketing reports of impulse-control disorders including gambling have been reported very rarely with antipsychotics, including brexpiprazole. Patients with a prior history of impulse-control disorders may be at increased risk and should be monitored carefully. It should be noted that impulse-control symptoms can be associated with the underlying disorder.

Lactose
REXULTI tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Use in hepatic impairment
In patients with hepatic impairment, dosage adjustment is required.

(See Section 5.2 Pharmacokinetic properties and Section 4.2 Dose and method of administration)

Use in renal impairment
In patients with renal impairment, dosage adjustment is required.

(See Section 5.2 Pharmacokinetic properties and Section 4.2 Dose and method of administration)

Use in the elderly

Clinical studies of REXULTI included limited numbers of subjects aged 65 and older to allow for determining whether they respond differently than younger subjects. Elderly subjects (older than 65 years old) exhibited similar brexpiprazole systemic exposure in comparison with adult subjects (18-45 years old) (See Section 5.2 Pharmacokinetic properties and Section 4.2 Dose and method of administration). Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo (see Section 4.4 Special warnings and precautions for use – Increased Mortality in Elderly Patients with Dementia-related Psychosis).

Paediatric use

Safety and effectiveness in patients under the age of 18 years has not yet been evaluated.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

REXULTI is predominantly metabolised by CYP3A4 and CYP2D6. Based on results of drug interaction trials, dose adjustment to half the maintenance dose is recommended for subjects administered strong CYP2D6 or CYP3A4 inhibitors. Based on estimations from the population pharmacokinetic analysis, CYP2D6 extensive metabolisers (EM) receiving both CYP3A4 and CYP2D6 inhibitors or CYP2D6 poor metabolisers (PM) receiving strong CYP3A4 inhibitors are expected to have an approximately 4-5 fold increase in brexpiprazole concentrations; therefore, the REXULTI dose should be reduced to ¼ of the recommended dosage in these situations (see Section 4.2 Dose and method of administration).

If REXULTI is used concomitantly with a strong CYP3A4 inducer (i.e. rifampicin), it is necessary to increase the dose by two fold and further adjust it based on clinical response (see Section 4.2 Dose and method of administration).

Quinidine and Other Strong CYP2D6 Inhibitors

Co-administration of a 2 mg single oral dose of REXULTI with quinidine (324 mg/day for 7 days), a potent inhibitor of CYP2D6, increased the AUC of brexpiprazole by 94%.

Ketoconazole and Other Strong 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 REXULTI increased the AUC of brexpiprazole by 97%.

Ticlopidine and Other CYP2B6 Inhibitors

Co-administration of a 2 mg single oral dose of REXULTI with ticlopidine (250 mg twice daily for 7 days), a potent inhibitor of CYP2B6, had no effect on the pharmacokinetics of brexpiprazole.

Rifampicin and Other CYP3A4 Inducers
Co-administration of rifampin (600 mg twice daily for 12 days), a potent CYP3A4 inducer, with a single 4 mg oral dose of REXULTI resulted in an approximate 31% and 73% decrease in brexpiprazole C_{max} and AUC.

Gastric Acid pH Modifiers
Co-administration of omeprazole (40 mg once daily, 5 days), a widely used proton pump inhibitor (PPI), with a single oral dose of REXULTI (4 mg) resulted in no effect on absorption of brexpiprazole. Other gastric acid pH modifiers (PPIs, H2 receptor antagonists, etc.) are also not expected to affect the absorption of brexpiprazole.

Potential for REXULTI to Affect Other Drugs
Based on results of *in vitro* studies, brexpiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolised by cytochrome P450 enzymes. Clinical studies show that oral REXULTI (2 mg/day, 11 days) had no effect on the metabolism of dextromethorphan (a CYP2D6 substrate), lovastatin (a CYP3A4 substrate) or bupropion (a CYP2B6 substrate). REXULTI does not affect absorption of drugs that are substrates of the BCRP transporter (rosuvastatin) or the P-gp transporter (fexofenadine).

As with other antipsychotics, caution should be used if brexpiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Effects on fertility
Drugs with D_2-antagonist properties are potential causes of hypothalamic-pituitary-gonadal axis disruption. Brexpiprazole was given once daily by oral gavage to female rats at doses of 0, 0.3, 3 or 30 mg/kg/day prior to mating with untreated males and continuing through conception and implantation. Prolonged diestrus and decreased fertility were observed at 3 and 30 mg/kg/day, with exposure (plasma AUC) ≥0.2 fold the clinical exposure at the 4 mg MRHD. At 30 mg/kg/day (AUC exposure 4-fold clinical exposure) a doubling of the mating phase and significantly increased preimplantation losses were seen. The no observed adverse effect level for brexpiprazole was 0.3 mg/kg/day (AUC exposure <0.2-fold clinical exposure).

Brexpiprazole was given once daily by oral gavage to male rats at doses of 0, 3, 10 or 100 mg/kg/day, with exposure (plasma AUC) up to 18-fold the clinical exposure at the 4 mg MRHD. Following 63 days of dosing (one spermatic cycle), treated males were cohabited with untreated females for a maximum of 14 days. No noticeable differences were noted in the duration of mating or fertility indices in any brexpiprazole treated group. Testicular lesions including atrophy of the seminiferous tubule were observed at doses of 30 mg/kg/day and higher (AUC exposure ≥ 6-fold clinical exposure) in repeat-dose toxicity studies, and a decrease in sperm in the epididymis was observed at 300 mg/kg/day (AUC exposure 37-fold clinical exposure) with minimal incidence (2 of 15 rats).

Use in Pregnancy (Category C)

Safe use of REXULTI during pregnancy or lactation has not been established. Therefore, use of REXULTI 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.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk of extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

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

Animal data

Brexpiprazole was not teratogenic and did not cause adverse developmental effects in embryofetal developmental toxicity studies in which pregnant rats and rabbits were given brexpiprazole during the period of organogenesis at oral doses up to 30 mg/kg/day (with respective exposures (plasma AUC) 4-fold and 7-fold the clinical exposure at the 4 mg/day MRHD).

In the rabbit study an oral dose that induced severe maternal toxicity (150 mg/kg/day, AUC exposure 21-fold clinical exposure) was associated with decreased body weight, retarded ossification, and increased incidences of visceral and skeletal variations in fetuses.

When pregnant rats were administered brexpiprazole orally during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 30 mg/kg/day (plasma AUC exposure 4-fold exposure at the 4 mg/day MRHD); the no-effect dose was 10 mg/kg/day (exposure similar to clinical exposure).

Use in lactation

Brexpiprazole and/or its metabolites was excreted in milk of rats during lactation, with milk levels about 1-2 fold maternal blood levels. It is not known whether brexpiprazole or its metabolites are excreted in human milk. Because of the potential for serious, potentially long-lived, 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.

4.7 Effects on ability to drive and use machines

As with other antipsychotics that have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery including motor vehicles until they are certain that REXULTI therapy does not affect them adversely.

In the short-term, placebo-controlled clinical trials in patients with schizophrenia, somnolence (including sedation and hypersomnia) was reported in 5% of REXULTI-treated patients compared to 4% of placebo-treated patients.

4.8 Adverse effects (Undesirable effects)

The following findings are based on the two 6-week, placebo-controlled, fixed-dose clinical trials (Trials 1 and 2) in schizophrenia in which REXULTI was administered at daily doses of 1 mg, 2 mg and 4 mg (n=852), and the long-term maintenance trial (Trial 3) with REXULTI 1-4mg/day (n= 97)

Common Adverse Reactions: There are no common adverse reactions that meet the criteria "incidence ≥5% and at least twice the rate of placebo" in Trials 1 and 2, the 6-week, placebo-controlled, fixed-dose trials, or Trial 3, the long-term maintenance trial.

Adverse reactions associated with REXULTI (incidence of 2% or greater and REXULTI incidence greater than placebo incidence) that occurred during acute therapy (up to 6 weeks in subjects with schizophrenia) and long-term therapy (up to 52 weeks) are shown in Table 1 and Table 2, respectively.

Table 1 Adverse Reactions Reported in ≥2% of REXULTI-treated Patients and that Occurred at Greater Incidence than Placebo-treated Patients in Fixed-dose Trials (Trials1 and 2)[a]

	REXULTI (brexpiprazole, mg/day)				
System Organ Class MedDRA Preferred Term	**1 mg (N=120) %**	**2 mg (N=368) %**	**4 mg (N=364) %**	**ALL (N=852) %**	**Placebo (N=368) %**
Gastrointestinal disorders					
Diarrhoea	0.8	3.3	3.3	2.9	1.9
Dyspepsia	5.8	2.4	3.0	3.2	1.9
Toothache	1.7	1.9	3.0	2.3	2.2
Investigations					
Weight increased	3.3	3.5	4.4	3.9	1.6
Blood creatine phosphokinase increased	4.2	1.9	2.2	2.3	1.1
Musculoskeletal and connective tissue disorders					
Back pain	0.8	2.2	3.0	2.3	2.2
Pain in extremity	3.3	1.6	1.9	2.0	0.5
Nervous system disorders					
Akathisia	4.2	4.6	6.9	5.5	4.6
Tremor	1.7	2.4	2.7	2.5	0.5
Sedation	1.7	1.6	2.7	2.1	0.8

[a] *Adverse events listed in the table are those reported with a frequency ≥ 2% in the REXULTI ALL group (pooled 1, 2 and 4 mg group) and higher than that in the placebo group*

Table 2 TEAEs that Occurred in at Least 2% of Subjects in REXULTI Group and Greater than in Placebo Group in Trial 3 (Randomised Double-blind Withdrawal Phase)

System Organ Class MedDRA Preferred Term	REXULTI (brexpiprazole) (N=97) n (%)	Placebo (N=104) n (%)
Gastrointestinal Disorders		
Toothache	3.1	1.0
Metabolism And Nutrition Disorders		
Decreased Appetite	2.1	0.0
Musculoskeletal And Connective Tissue Disorders		
Muscle Spasms	2.1	0.0
Musculoskeletal Pain	2.1	1.0
Nervous System Disorders		
Tremor	3.1	0.0
Skin And Subcutaneous Tissue Disorders		
Pruritus	2.1	0.0

Discontinuations due to TEAEs occurred at less than half the rate in the REXULTI group (5.2%) compared with the placebo group (11.5%) in the double-blind maintenance phase of Trial 3. No subjects discontinued due to weight gain or akathisia.

Selected Adverse Events

Extrapyramidal Symptoms

In Trials 1 and 2, the incidence of EPS-related events, excluding akathisia events, was 5.1% for REXULTI-treated subjects versus 3.5% for placebo-treated subjects. The incidence of akathisia events (akathisia, psychomotor hyperactivity) for REXULTI-treated subjects was 5.4% versus 4.9% for placebo-treated subjects. Akathisia was reported in all treatment arms and were more often during Weeks 1 through 3 and was mild to moderate in severity.

In Trials 1 and 2, data were objectively collected on the Simpson Angus Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia. The mean changes from baseline at last visit for REXULTI-treated subjects for the SAS, BARS and AIMS were comparable to those for placebo-treated subjects (-0.10, 0.02 and -0.08 compared to 0.00, 0.01 and -0.07 respectively).

Similarly, in Trial 3, the mean changes from baseline at last visit for REXULTI-treated subjects for the SAS, BARS and AIMS were comparable to those for the placebo-treated subjects.

Dyslipidaemia

Undesirable alterations in lipids have been observed in subjects treated with atypical antipsychotics.

In Trials 1 and 2, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in REXULTI- and placebo-treated subjects. Table 3 shows the proportions of subjects with changes in fasting triglycerides.

Table 3 Change in Fasting Triglycerides in Trials 1 and 2

Proportion of Subjects with Shifts Baseline to Post-Baseline				
	Placebo	**1 mg/day**	**2 mg/day**	**4 mg/day**
Triglycerides ***Normal to High*** (<150 mg/dL to ≥200 and <500 mg/dL)	6% (15/253)*	10% (7/72)*	8% (19/232)*	10% (22/226)*
Normal/Borderline to Very High (<200 mg/dL to ≥500 mg/dL)	0% (0/303)*	0% (0/94)*	0% (0/283)*	0.4% (1/283)*

* denotes n/N where N=the total number of subjects who had a measurement at baseline and at least one post-baseline result. n=the number of subjects with a shift.

In Trial 3, no clinically meaningful differences between treatment groups were observed for the incidences of metabolic parameters meeting potentially clinically relevant criteria.

In the long-term open-label studies, the mean change from baseline to last visit in fasting triglycerides was -2.14 mg/dL (N=1123).

Weight Gain

The percentage of subjects in short-term Trials 1 and 2 who had a potentially clinically relevant increase in body weight (≥7%) was 10.5% and 10.2% in the REXULTI 2 and 4 mg/day groups, respectively, compared with 4.1% in the placebo group. The mean body weight increase in the short-term trials at last visit was 1.2 kg for both the REXULTI 2 and 4 mg/day groups compared with 0.2 kg in the placebo group.

During Trial 3 the proportion of subjects with a ≥7% increase in body weight at last visit was 3.1 % in the REXULTI group compared to 1.0% in the placebo group.

In the long-term, open-label schizophrenia studies, the mean change in body weight from baseline to last visit was 1.1 kg at last observation.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Other adverse reactions (<2% frequency and greater than for placebo) in the short-term, fixed- dose placebo-controlled trials and the long-term maintenance trial in subjects with schizophrenia are shown below. The following listing does not include adverse reactions: 1)

already listed in previous tables or elsewhere in the labelling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have clinically significant implications.

Cardiovascular Disorders: Sinus Bradycardia, Atrioventricular Block First Degree, Palpitations

Endocrine Disorders: Hyperprolactinaemia

Eye Disorders: Vision Blurred, Blepharospasm

Gastrointestinal Disorders: Dry Mouth, Abdominal Pain, Flatulence, Dental Caries, Abdominal Distension, Gastrooesophageal Reflux Disease

General Disorders & Administration Site Conditions: Fatigue, Asthenia

Infections and Infestations: Upper Respiratory Tract Infection

Investigations: Hepatic Enzyme Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia, Musculoskeletal Pain, Musculoskeletal Stiffness

Nervous System Disorders: Dizziness, Dyskinesia, Parkinsonism, Psychomotor Activity

Psychiatric Disorders: Abnormal Dreams, Bruxism

Skin and Subcutaneous Tissue Disorders: Rash

Vascular Disorders: Hypertension, Flushing, Hypotension

Abnormal Hematologic and Clinical Chemistry Findings

No clinically relevant mean changes from baseline in serum chemistry, haematology, urinalysis, or other laboratory test (insulin, fasting insulin and prolactin) results were observed during the clinical trials with REXULTI.

Post-Marketing Adverse Drug Reactions

Post-marketing reports of impulse-control disorders including gambling have been reported very rarely with antipsychotics, including REXULTI. While absolute causality has not been established, Lundbeck Australia Pty Ltd will continue to monitor the situation closely.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

No specific information is available on the treatment of overdose with REXULTI. Gastric lavage and treatment with an emetic may be useful immediately after overdose. An electrocardiogram should be obtained in case of overdosage 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.

For information on the management of overdose, contact the Poison Information Centre (Tel: 13 11 26 for Australia).

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral REXULTI, 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 REXULTI. Although there is no information on the effect of haemodialysis in treating an overdose with REXULTI, haemodialysis is unlikely to be useful in overdose management since brexpiprazole is highly bound to plasma proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Brexpiprazole has high affinity (K_i<5 nM) for multiple monoaminergic receptors, including serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_7, dopamine D_2 and D_3, and noradrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole acts as a partial agonist at 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole exhibits moderate affinity for histamine H_1 receptors (19 nM) and very weak affinity for muscarinic M_1 receptors (67% inhibition at 10 µM). Dose-response occupancy and brain/plasma exposure relationship were determined *in vivo* or *ex vivo* for D_2/D_3, 5-HT_{2A}, 5-HT_{1A}, 5-HT_6, and 5-HT_7 receptors as well as for the 5-HT transporter in preclinical studies. These results are consistent with the relative *in vitro* binding affinities and indicate that brexpiprazole has potent activity at several targets in the central nervous system (CNS) at relevant plasma exposures.

Despite low intrinsic activity at D_2 receptors and potent antipsychotic effect, brexpiprazole showed low liability for catalepsy (animal model for extrapyramidal side effects) and for inducing tardive dyskinesia (indicative of increased sensitivity of the post-synaptic D_2 receptors). The potencies of these effects were similar to or lower than those of other antipsychotic agents. Brexpiprazole showed a relatively low binding affinity for H_1 receptors compared with that for D_2 receptors, implying a low potential for H_1 receptor-related sedative effects.

In a thorough QTc study in patients with schizophrenia or schizoaffective disorder, REXULTI did not prolong QTcI or QTcF after 12 days dosing at the clinical (4 mg/day) or at a supra-therapeutic (12 mg/day) dose, and no correlation was observed between brexpiprazole concentrations and QTcI or QTcF prolongation. Based on *in vitro* data the risk of hERG channel-mediated effects at the clinical dose appears to be low. There are no data on the potential for QTc prolongation via effects on the I_{Ks} (KCNQ1-KCNE1 complex) and Na_y (SCN5A) ion currents.

Mechanism of action

REXULTI is a novel atypical antipsychotic agent, which has pharmacological activity as a serotonin-dopamine activity modulator. While the precise mechanism of action of brexpiprazole in treating schizophrenia is not fully understood, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has 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: 0.1-0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic α1B/2C receptors with affinity in the same sub-nanomolar Ki range (Ki: 0.2-0.6 nM). The 5-$HT_{1A/D2}$ receptor partial agonist activity in combination with the 5-HT_{2A} and $\alpha_{1B/2C}$ receptor antagonism of brexpiprazole may contribute to its antipsychotic effect.

Clinical trials

The efficacy of REXULTI in the treatment of adults with schizophrenia was demonstrated in two 6-week, randomised, double-blind, placebo-controlled, fixed-dose clinical trials (Trials 1 and 2) and one long-term maintenance trial (Trial 3) in subjects who met DSM-IV-TR criteria for schizophrenia.

In the two fixed-dose trials, subjects were randomised to REXULTI 2 mg once daily, 4 mg once daily or placebo. Subjects in the REXULTI groups initiated treatment at 1 mg once daily on Day 1. The REXULTI dosage was increased to 2 mg once daily on Day 5. On Day 8, the dosage was either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for the 5 remaining weeks. Trials 1 and 2 also included a low dose group, 0.25 mg/day and 1 mg/day REXULTI, respectively, but these dose groups were not included in the primary analysis.

The primary efficacy endpoint for both trials was the change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); the total PANSS scores range from 30 (best) to 210 (worst). The key secondary endpoint of both trials was the change from baseline to Week 6 in Clinical Global Impression – Severity of Illness Scale (CGI-S) score, a validated clinician-rated scale that measures the subject's current illness state and overall clinical state on a 1- (normal, not at all ill) to 7-point (extremely ill) scale. Other secondary endpoints included the Personal and

Social Performance scale (PSP), a validated clinician-rated scale that measures personal and social functioning.

In Trials 1 and 2, REXULTI 2 mg/day and 4 mg/day demonstrated efficacy with clinically meaningful changes in several efficacy endpoint measures.

At endpoint, REXULTI 4 mg was consistently superior to placebo in both fixed-dose trials, reducing disease symptoms and severity as assessed using the primary endpoint, the PANSS total score. The onset of action with REXULTI occurred as early as Week 1. In Trial 1, a significant improvement was achieved in PANSS total score by Week 1 for 2 mg/day ($p=0.0139$) and Week 2 for 4 mg/day ($p=0.0009$). In Trial 2, a significant improvement was achieved in PANSS total score by Week 1 and then from Week 3 onwards with 4 mg/day ($p<0.05$).

Results for the primary efficacy endpoint for Trials 1 and 2 are shown in Table 4.

Figure 1 shows the time course of response based on the primary efficacy measure (PANSS) in Trial 1.

Examination of population subgroups based on age, sex and race did not show any statistical evidence of differential responsiveness.

Table 4 Primary Efficacy Results for 6-Week Trials in Schizophrenia (Trials 1 and 2)

Trial	Treatment Group	N	Primary Efficacy Measure: PANSS			
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	LS Means Difference[a] (95% CI)	p-value
1	REXULTI (2 mg/day)*	180	95.85 (13.75)	-20.73 (1.55)	-8.7 (-13.1, -4.4)	<.0001
	REXULTI (4 mg/day)*	178	94.70 (12.06)	-19.65 (1.54)	-7.6 (-12.0, -3.1)	0.0006
	Placebo	178	95.69 (11.46)	-12.01 (1.60)	--	- -
2	REXULTI (2 mg/day)	179	96.30 (12.91)	-16.61 (1.49)	-3.1 (-7.2, 1.1)	0.1448
	REXULTI (4 mg/day)*	181	94.99 (12.38)	-20.00 (1.48)	-6.5 (-10.6, -2.4)	0.0022
	Placebo	180	94.63 (12.84)	-13.53 (1.52)	--	-

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
* Treatment statistically significantly superior to placebo
[a] Difference (drug minus placebo) in least-squares mean change from baseline, at Week 6.

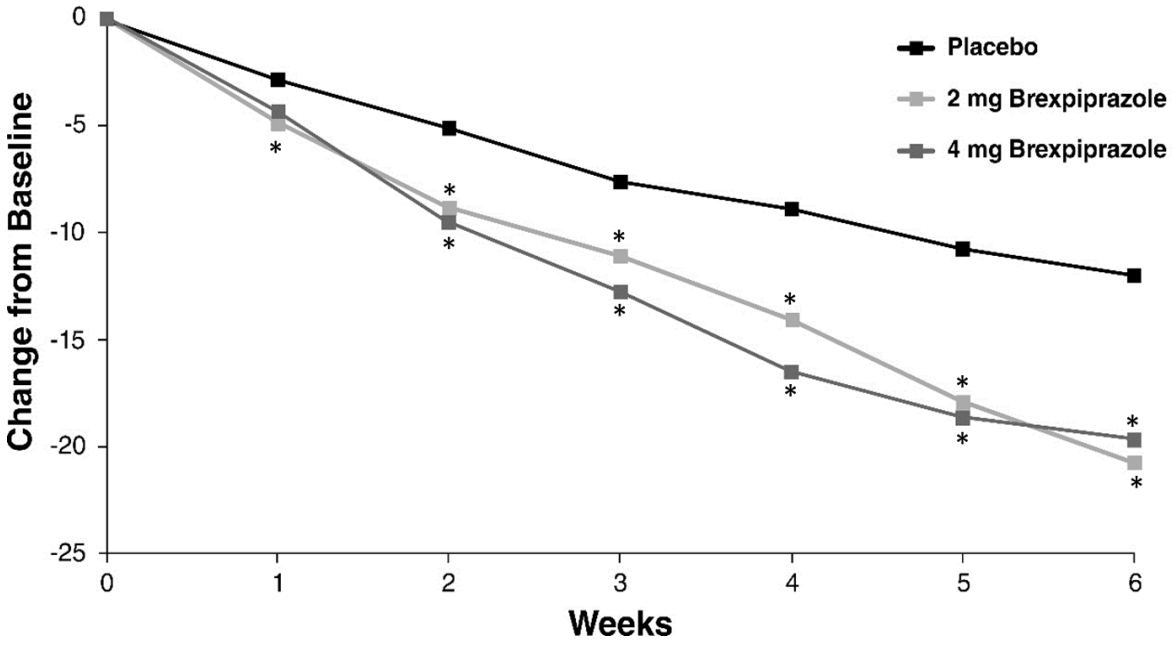


Figure 1 Change from Baseline in PANSS Total Score by Trial Visit (Week) - Trial 1

In addition, REXULTI 2 mg/day and 4 mg/day demonstrated superiority to placebo in the key secondary endpoint, CGI-S score. Significant improvements in CGI-S score were seen as early as Week 2 in Trial 1 and Week 3 in Trial 2.

In Trial 1, REXULTI also demonstrated superiority to placebo across several pre-specified secondary endpoints, including: the change from baseline to Week 6 in PSP score (2 mg/day), PANSS Positive Subscale score (2 mg/day and 4 mg/day) and PANSS Negative Subscale score (2 mg/day and 4 mg/day,); Clinical Global Impression - Improvement scale (CGI-I) score (2 mg/day and 4 mg/day); response rate at Week 6 (2 mg/day and 4 mg/day); and discontinuation for lack of efficacy (4 mg/day).

In Trial 2, REXULTI 4 mg/day demonstrated superiority to placebo in the change from baseline to Week 6 in PSP score, PANSS Positive Subscale score and PANSS Negative Subscale score; CGI-I score; response rate at Week 6.

Thus, the secondary endpoint results for CGI-S, PSP, CGI-I, PANSS Positive Subscale, PANSS Negative Subscale and response rate support the superiority and clinically meaningful effect of REXULTI compared to placebo.

Additionally, both trials had high overall completion rates, which were higher in the REXULTI groups than in the placebo group.

Results for the secondary efficacy endpoints for Trials 1 and 2 are shown in Table 5.

Table 5 Secondary Efficacy Results for 6-Week Trials in Schizophrenia (Trials 1 and 2)

Secondary Efficacy Endpoint	Trial 1		Trial 2	
	REXULTI 2 mg (N=180)	**REXULTI 4 mg (N=178)**	**REXULTI 2 mg (N=179)**	**REXULTI 4 mg (N=181)**
CGI-S score, LSMD[a] (p-value)	-0.33 (**0.0056**)	-0.38 (**0.0012**)	-0.19 (0.1269)	-0.38 (**0.0015**)
PSP score, LSMD[a] (p-value)	2.89 (**0.0250**)	2.46 (0.0557)	2.00 (0.1286)	4.59 (**0.0005**)
PANSS Positive score, LSMD[a] (p-value)	-2.22 (**0.0029**)	-2.44 (**0.0010**)	-0.47 (0.5101)	-1.70 (**0.0166**)
PANSS Negative score, LSMD[a] (p-value)	-1.78 (**0.0007**)	-1.41 (**0.0069**)	-0.77 (0.1547)	-1.22 (**0.0231**)
CGI-I score, Mean Difference[b] (p-value)	-0.54 (**0.0002**)	-0.50 (**0.0004**)	-0.30 (0.0422)	-0.49 (**0.0009**)
Response[c] Rate				
% Responders REXULTI	47.78%	46.07%	38.55%	49.72%
Placebo	30.34 %		31.67%	
Relative Risk[d] (p-value)	1.59 (**0.0004**)	1.48 (**0.0032**)	1.22 (0.1680)	1.54 (**0.0006**)

[a] Difference (drug minus placebo) in least-squares mean change from baseline at Week 6.

[b] Derived from the Cochran-Mantel-Haenszel (CMH) row mean score test.

[c] Defined as a ≥30% reduction from baseline in PANSS total score or a CGI-I score of 1 or 2, using LOCF at Week 6.

[d] Derived from the CMH general association test, stratified by trial site.

The long-term trial (Trial 3) was a randomised, double-blind, placebo-controlled trial to assess the efficacy, safety, and tolerability of REXULTI 1 - 4 mg/day as maintenance treatment in adults with schizophrenia. The primary endpoint was the time to impending relapse. The key secondary endpoint was the percentage of subjects with impending relapse, and other secondary endpoints included the mean change in PANSS total score and CGI-S score.

A pre-specified interim analysis demonstrated a statistically significantly longer time to impending relapse in subjects randomised to the REXULTI group (1 - 4 mg/day) compared to subjects randomised to the placebo group ($p = 0.0008$, log-rank test) and the trial was subsequently terminated early because maintenance of efficacy was demonstrated. The final analysis also demonstrated a statistically significantly longer time to impending relapse in subjects randomised to the REXULTI group compared to subjects randomised to the placebo group ($p < 0.0001$, log-rank test). The Kaplan-Meier curves of the cumulative proportion of subjects who relapsed during the double-blind treatment phase for the REXULTI and placebo groups in the final analysis set are shown in Figure 2. For the final analysis, the hazard ratio from the Cox proportional hazard model for the placebo to REXULTI comparison was 3.42 (95% CI: 1.82, 6.41); thus, subjects in the placebo group had a 3.42-fold greater risk of experiencing impending relapse than the subjects in the REXULTI group.

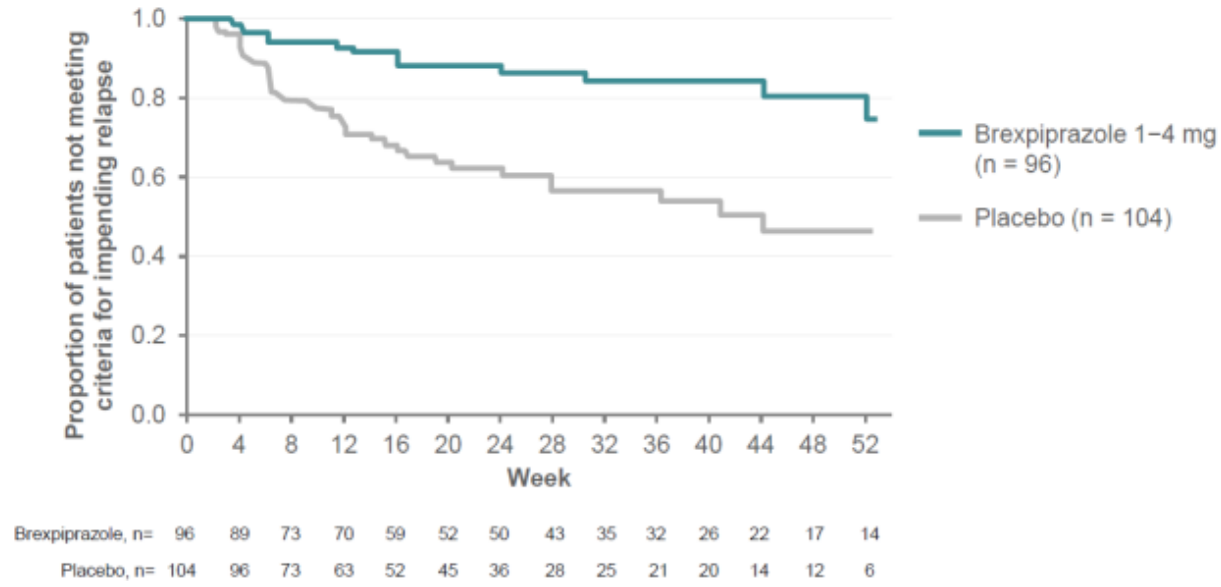


Figure 2 Kaplan-Meier Curves of Time to Impending Relapse (Double-blind Maintenance Phase Efficacy Sample) – Final Analysis, Trial 3

The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was statistically significantly lower with the REXULTI group compared with the placebo group in both the interim and final analyses (15.38% vs 37.08%, p = 0.0016 and 13.54% vs 38.46%, p < 0.0001, respectively).

In the double-blind maintenance phase, the PANSS Total score and CGI-S score both showed supportive patterns of stability of symptoms, which were maintained over time with REXULTI treatment, whereas they worsened with placebo treatment (p = 0.0011, p = 0.0006, for the comparison of REXULTI vs placebo for PANSS total score and CGI-S, respectively).

5.2 Pharmacokinetic properties

Absorption

Brexpiprazole is well absorbed after administration of REXULTI tablets, with peak plasma concentrations occurring within 4.0 hours after single-dose administration; the absolute oral bioavailability of the tablet formulation is 95.1%. Brexpiprazole steady-state concentrations are attained within 10-12 days of dosing. REXULTI can be administered with or without food. Administration of a REXULTI 4 mg 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) increased in proportion to the dose administered. *In vitro* studies did not indicate that brexpiprazole is a substrate of efflux transporters such as MDRI (P-gp) and BCRP.

Distribution

The volume of distribution of brexpiprazole following intravenous administration is high (1.56±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, or digoxin.

Metabolism and Excretion

Based on *in vitro* metabolism studies of brexpiprazole using recombinant human cytochrome P450 (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4), the metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6. Based on the results of *in vitro* data, brexpiprazole showed little to no inhibition of CYP450 isozymes. The *in vitro* inhibitory potential of brexpiprazole on MDR1 (P-gp), OAT1, OAT3, OCT2, multidrug and toxin extruders (MATE1), MATE2-K, OATP1B1, OATP1B3, and OCT1 has also been evaluated; brexpiprazole was only identified as a potential inhibitor of the BCRP efflux transporter, but was not considered to be an inhibitor of the other tested transporters.

In vivo, brexpiprazole is metabolised primarily by CYP3A4 and CYP2D6 enzymes. After single- and multiple-dose administrations, brexpiprazole and a major metabolite, DM-3411, are the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represents 23.1-47.7% 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.

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. The apparent oral clearance of brexpiprazole after once-daily tablet administration is 19.8 (±11.4) mL/h/kg. After multiple once-daily administrations of REXULTI, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.

Special Populations

Age/Sex

After single-dose administration of REXULTI (2 mg), healthy elderly subjects (older than 65 years old) exhibited similar brexpiprazole systemic exposure (C_{max} and AUC) in comparison with adult subjects (18-45 years old) and female subjects exhibited approximately 40-50% higher brexpiprazole systemic exposure (C_{max} and AUC) in comparison with male subjects. Population pharmacokinetic evaluation identified age and female sex as statistically significant covariates affecting brexpiprazole pharmacokinetics and not considered clinically relevant.

Race

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

CYP2D6 Poor Metabolisers
Approximately 8% of Caucasians and 3–8% of Blacks/African Americans lack the capacity to metabolise CYP2D6 substrates and are classified as PM, whereas the rest are EM. Population pharmacokinetic evaluation shows that CYP2D6 PMs have 47% higher exposure to brexpiprazole compared to EMs. (See Section 4.2 Dose and method of administration)

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

Hepatic Impairment
Patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) generally had higher exposure to brexpiprazole than patients with normal hepatic function; therefore, the recommended maximum dose should be reduced. In subjects 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.

Renal Impairment
Patients with impaired renal function (CLcr <60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function; therefore, the recommended maximum dose should be reduced. In subjects with severe renal impairment (CLcr <30 mL/min), the AUC of oral brexpiprazole (2 mg single dose) compared to matched healthy subjects, increased 68% while its C_{max} did not change.

5.3 Preclinical safety data

Genotoxicity
The mutagenic potential of brexpiprazole was tested in the *in vitro* bacterial reverse mutation assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster ovary (CHO) cells, the *in vivo* micronucleus assay in rats, and the unscheduled DNA synthesis assay in rats. Brexpiprazole was mutagenic and induced chromosomal aberrations in mammalian cells *in vitro* but only at cytotoxic concentrations. No mutagenicity or genotoxicity was observed in the higher tier *in vivo* studies. Brexpiprazole is unlikely to affect the mitotic spindle or kinetochores. Based on the weight of evidence, brexpiprazole is not considered to present a genotoxic risk to humans.

Carcinogenicity
The lifetime carcinogenic potential of brexpiprazole was evaluated in two year oral (gavage) studies in ICR mice and Sprague-Dawley rats. Brexpiprazole was administered to mice at doses of 0.75, 2 and 5 mg/kg/day, with plasma AUC exposures of 0.4-4-fold (males) and 0.2-1-fold (females) clinical exposure at the 4 mg/day MRHD. There was no increase in the incidence of tumours in males at any dose group. In female mice, there was an increased

incidence of mammary gland adenocarcinoma and adenosquamous carcinoma, and pars distalis adenoma of the pituitary gland, at all doses. Brexpiprazole was administered to rats at doses of 1, 3 and 10 mg/kg/day (males) or 3, 10 and 30 mg/kg/day (females), with plasma AUC exposure up to 1-fold (males) and 6 fold (females) clinical exposure at the 4 mg/day MRHD. Long-term administration of brexpiprazole to rats did not induce neoplastic lesions.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be secondary to D_2-antagonist-induced hyperprolactinaemia. The potential for increasing serum prolactin level of brexpiprazole was shown in both mice and rats. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refer to Section 2 - Qualitative and quantitative composition.

6.2 Incompatibilities

Refer to Section 4.5 – Interactions with other medicines and other forms of interactions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

REXULTI tablets are packaged in polyvinyl chloride (PVC)/aluminium foil blisters.

Pack sizes of 30 film-coated tablets (all strengths). Starter pack size of 10 film-coated tablets: 1 mg and 2 mg.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

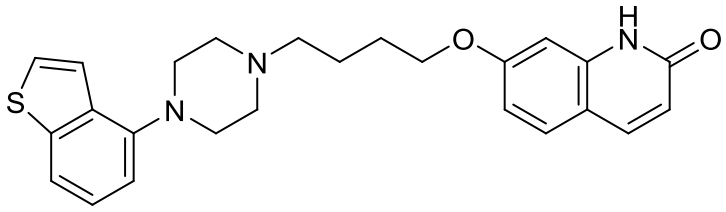
6.7 Physicochemical properties

Brexpiprazole is 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butyloxy}quinolin-2(1*H*)-one.

Molecular formula: $C_{25}H_{27}N_3O_2S$
Molecular weight: 433.57

Brexpiprazole is nonhygroscopic, with white to off-white crystals or crystalline powders, and a melting point of 183°C (decomposition). It is practically insoluble in water, and the solubility of the drug substance is 0.56 mg/mL at pH 2.

Chemical structure



CAS number

913611-97-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 May 2017

10 DATE OF REVISION

21 August 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformatted in line with the revised Australian form for providing product information.

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