SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

REXULTI 0,5 mg Film-coated Tablets

REXULTI 1 mg Film-coated Tablets

REXULTI 2 mg Film-coated Tablets

REXULTI 3 mg Film-coated Tablets

REXULTI 4 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each REXULTI 0,5 mg tablet contains 0,5 mg brexpiprazole

Each REXULTI 1 mg tablet contains 1 mg brexpiprazole

Each REXULTI 2 mg tablet contains 2 mg brexpiprazole

Each REXULTI 3 mg tablet contains 3 mg brexpiprazole

Each REXULTI 4 mg tablet contains 4 mg brexpiprazole.

REXULTI tablets contain sugar. Lactose monohydrate per tablet :

0,5 mg tablet contains 47,9 mg;

1 mg tablet contains 47,4 mg; 2 mg tablet contains 46,4 mg;

3 mg tablet contains 45,4 mg; 4 mg tablet contains 44,4 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

0,5 mg tablets: Light orange round film-coated tablets, debossed with “BRX” and “0.5” on one side

1 mg tablets: Light yellow round film-coated tablets, debossed with “BRX” and “1” on one side

2 mg tablets: Light green round film-coated tablets, debossed with “BRX” and “2” on one side

3 mg tablets: Light purple round film-coated tablets, debossed with “BRX” and “3” on one side

4 mg tablets: White to off-white round film-coated tablets, debossed with “BRX” and “4” on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

REXULTI is indicated in adult patients for treatment of schizophrenia

4.2 Posology and method of administration

For oral use once daily with or without food

Posology

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 through Day 7, 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.

Special populations

Dosing Precautions

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 (See section 4.4 and 5.2).

Dosing Adjustment for Renal Impairment

For patients with moderate, severe or end-stage renal impairment (creatinine clearance CLcr < 60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia. (See sections 4.4 and 5.2).

Dosing Modifications for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP Inhibitors/Inducers (See section 4.3)

Factors	**Adjusted Dose**
CYP2D6 Poor Metabolizers	
Known CYP2D6 poor metabolizers	Administer half of the usual dose
Known CYP2D6 poor metabolizers 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.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients (see section 6.1).

Hypersensitivity reactions have included rash, angioedema, facial swelling, anaphylaxis and urticaria.

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 antipsychotics are at an increased risk of death compared to placebo.

Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), in patients taking atypical antipsychotic drugs (including risperidone, aripiprazole, olanzapine, and quetiapine), 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 the placebo group.

REXULTI is not approved for the treatment of dementia-related psychosis.

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 patients.

Suicidal Risk

The possibility of a suicide attempt is inherent in psychotic illnesses. Suicidal ideation and attempt have been reported during use of REXULTI. Close supervision and appropriate clinical management of high-risk patients should accompany treatment with REXULTI.

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 medicines 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 medicines including REXULTI must be discontinued.

If a patient requires treatment with antipsychotic medicines after recovery from NMS, the potential reintroduction of medicine should be carefully considered.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic medicines.

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 medicines 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. 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.

Patients who develop symptoms of hyperglycaemia during treatment with REXULTI should undergo fasting blood glucose testing.

Weight Gain and Dyslipidaemia

Antipsychotic medicines have been associated with metabolic changes, including weight gain and dyslipidaemia. Clinical monitoring of weight is recommended (see section 4.8).

Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and/or post-marketing experience, leukopenia and neutropenia have been reported temporally related to atypical antipsychotic medicines. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) or a history of drug-induced leukopenia or neutropenia.

Patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or 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 < 1 000/mm3) should discontinue REXULTI and have their WBC followed until recovery.

QT prolongation

QT prolongation can develop in patients treated with antipsychotics, such as REXULTI. Caution should be exercised when REXULTI is prescribed in patients with known cardiovascular disease, family history of QT prolongation, electrolyte imbalance or in concomitant use with other medicinal products thought to prolong the QT interval.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotics, such as REXULTI. 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.

Orthostatic Hypotension and Syncope

Adverse reactions related to orthostatic hypotension can include dizziness, light headedness and tachycardia and have been reported during antipsychotic use, including use of REXULTI. Generally, these risks are greatest at the beginning of treatment 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, hypovolaemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischaemia, 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).

Falls

Antipsychotics, including REXULTI, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, fall risk assessments, when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy, should be completed.

Seizures

REXULTI should be used with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Seizures have been reported during use of REXULTI. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. 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. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. REXULTI and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Impulse-Control Disorders/Compulsive Behaviours

Post-marketing reports of impulse-control disorders including gambling have been reported in patients treated with antipsychotic medicines such as REXULTI with partial agonist activity at dopamine receptors. Patients with a prior history of impulse-control disorders may be at increased risk and should be monitored carefully. Because patients may not recognize 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 REXULTI. It should be noted that impulse-

control symptoms can be associated with the underlying disorder. Compulsive behaviours may result in harm to the patient and others if not recognized.

Special populations

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 maximum recommended dosage is 3 mg once daily for patients with schizophrenia. (see section 4.2 and 5.2).

Renal Impairment

Patients with impaired renal function (CLcr < 60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function; therefore, the maximum recommended dosage is 3 mg once daily for patients with schizophrenia. (see section 4.2 and 5.2).

Paediatric Use

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

Geriatric Use

Clinical studies of REXULTI did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

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, or cardiac function, and of concomitant disease or other medicine therapy. (See section 5.2).

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

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: Special Populations).

Patients with lactose intolerance

Patients with rare hereditary problems of galactose intolerance, eg. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should be aware that REXULTI tablets contain lactose.

4.5 Interactions with other medicines and other forms of interactions

Brexpiprazole is predominantly metabolized by CYP3A4 and CYP2D6.

Based on results of medicine interaction trials, dosing should be adjusted to half the recommended dose for patients administered with strong CYP2D6 or CYP3A4 inhibitors.

Based on estimations from the population PK analysis, CYP2D6 EMs receiving both CYP3A4 and CYP2D6 inhibitors or CYP2D6 PMs receiving strong CYP3A4 inhibitors are expected to have approximately 4- 5 fold increase in brexpiprazole concentrations;

subsequently REXULTI dose should be accompanied with reduction of its dose to ¼ of the recommended dosage in these situations (see section 4.2).

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

Medicines

Potential for other medicines to affect REXULTI:

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 % (see section 4.2).

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 % (see section 4.2).

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 brexpiprazole.

Rifampicin and Other 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 REXULTI resulted in an approximate 31 % and 73 % decrease in brexpiprazole Cmax and AUC (see section 4.2).

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 metabolized by cytochrome P450 enzymes.

Clinical studies show that oral REXULTI (2 mg/day, 5 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 medicines that are substrates of Breast Cancer Resistance Protein (BCRP) transporter (rosuvastatin) and P-glycoprotein (PgP) transporter (fexofenadine).

Food

Intake of food has no effect on the pharmacokinetics of brexpiprazole (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use of REXULTI during pregnancy or lactation has not been established; brexpiprazole is not recommended during pregnancy.

Women of childbearing potential should use effective contraception.

Neonates exposed to antipsychotic medicines during the third trimester of pregnancy are at risk for 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 hospitalization.

The effect of REXULTI on labour and delivery in humans is unknown.

Parturition in rats was not affected by brexpiprazole.

Breastfeeding

Brexpiprazole was excreted into the milk of rats during lactation.

Because of the potential for serious adverse reactions in nursing infants, women taking REXULTI should not breastfeed their infants.

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

REXULTI has 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.

4.8 Undesirable effects

The following adverse reactions are discussed in more detail in section 4.4: Special warnings and precautions for use:

- Increased mortality in elderly patients with dementia-related psychosis
- Suicidal thoughts and behaviours in children, adolescents and young adults
- Cerebrovascular adverse reactions including stroke in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome (NMS)
- Tardive dyskinesia
- Impulse-control disorders/Compulsive behaviours
- Leukopenia, neutropenia, and agranulocytosis
- Orthostatic hypotension and syncope
- Falls
- Seizures
- Body temperature dysregulation

- Dysphagia

CLINICAL TRIAL DATA

Table 4 shows the incidence of adverse reactions that occurred in at least 2 % of patients treated with 2-4 mg REXULTI-treated group and observed more frequently than placebo.

Table 4 Adverse Reactions Reported in ≥ 2 % of REXULTI-treated Patients and that Occurred at Greater Incidence than Placebo-treated Patients in the Short-term, Placebo-Controlled Schizophrenia Clinical Trials

Gastrointestinal Disorders	
Common (≥ 1 % and < 10 %)	Diarrhoea, Nausea
Investigations	
Common (≥ 1 % and < 10 %)	Weight increased, Blood Creatine Phosphokinase Increased
Musculoskeletal and Connective Tissue Disorders	
Common (≥ 1 % and < 10 %)	Back pain
Nervous System Disorders	
Common (≥ 1 % and < 10 %)	Akathisia, Dizziness, Tremor

Adverse reactions that occurred < 2 % and the difference between REXULTI and placebo ≥ 0.5 % in the short-term; placebo-controlled schizophrenia clinical trials included abdominal pain upper, dental caries, flatulence, pain, blood pressure increased, blood triglycerides increased, pain in extremity, myalgia, sedation, cough and rash.

Extrapyramidal Symptoms

In the 6-week, placebo-controlled, fixed-dose schizophrenia studies for 2-4 mg REXULTI-treated patients, the incidence of reported EPS-related events, excluding akathisia events, was

12 % versus 10 % for placebo-treated patients. The incidence of akathisia events for REXULTI-treated patients was 6 % versus 5 % for placebo treated patients.

Clinical Chemistry Findings

Weight Gain

In the long-term, open-label schizophrenia studies, the mean change in body weight from baseline to last visit was 1,0 kg (N=1468). The proportion of patients with a ≥ 7 % increase in body weight at any visit was 17,9 % (226/1257) and with a ≥ 7 % decrease in body weight at any visit was 8,2 % (104/1257). Weight gain led to discontinuation of study medication in 0,4 % (5/1265) of patients.

Fasting Glucose

In the long-term, open-label schizophrenia studies, 7 % of patients with normal baseline fasting glucose experienced a shift from normal to high while taking REXULTI, 17 % of subjects with borderline fasting glucose experienced shifts from borderline to high.

Combined, 9 % of patients with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies. The mean change from baseline for fasting glucose to last visit in the long-term, open label trials was 2,35 [2,00] mg/dL.

Fasting Lipids

In the long-term open-label studies, shifts in baseline fasting cholesterol from normal to high were reported in 6 % (total cholesterol), 3 % (LDL cholesterol), and shifts in baseline from normal to low were reported in 20 % (HDL cholesterol) of patients taking REXULTI. Of patients with normal baseline triglycerides, 14 % experienced shifts to high, and 0,3 % experienced shifts to very high triglycerides. Combined, 0,5 % of patients with normal or

borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies. The mean changes from baseline for fasting HDL cholesterol, fasting LDL cholesterol, fasting cholesterol and fasting triglycerides to last visit in the long-term, open label trials were 0,89 [1,00] mg/dL, -0,97 [-1,00] mg/dL, 0,05 [0,00] mg/dL and -0,40 [-2,00] mg/dL, respectively.

Additional Findings Observed in Schizophrenia Clinical Trials

The adverse reactions reported in a 52-week maintenance phase of a randomized, placebo-controlled withdrawal trial in adults with schizophrenia were comparable with those reported in short-term, fixed-dose trials for schizophrenia.

Post marketing

The following adverse reaction has been reported during the post marketing period with REXULTI. The frequency of the reported adverse reaction is unknown:

- Nervous system disorders: Neuroleptic malignant syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the ‘6.04 Adverse Drug Reactions Reporting Form found online under SAHPRA’s publications: http://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific information is available on the treatment of overdose with REXULTI. An electrocardiogram should be obtained in case of over dosage 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.

Consult a certified poison control center for up to date guidance and advice.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral REXULTI, decreased brexpiprazole Cmax 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 (See section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

CATEGORY AND CLASS

A 2.6.5 Antipsychotics – miscellaneous structure

Brexpiprazole has high affinity (Ki <5 nM) for multiple monoaminergic receptors including serotonin 5- HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, dopamine D_2, D_3, and noradrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors.

Brexpiprazole acts as a partial agonist at the 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 a moderate affinity for histamine H_1 receptor (19 nM) and a very weak affinity for muscarinic M_1 receptor (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 a low intrinsic activity at the D_2 receptor and potent antipsychotic effect, brexpiprazole showed low liability for catalepsy (animal model for extrapyramidal side effect) and for inducing tardive dyskinesia (indicative of post-synaptic D_2 receptors increased sensitivity). The potencies of these effects were similar or lower to other antipsychotic agents.

Brexpiprazole showed very low tendency to induce ptosis (animal model for sedation) and its relatively low binding affinity to H_1 receptor compared to that for D_2 receptor would further suggest a low potential for H_1-related sedative effect.

Brexpiprazole does not prolong mean QTcI or QTcF at the clinical (4 mg) or at a supra-therapeutic (12 mg) dose range, and no correlation has been observed between brexpiprazole concentrations and QTcI or QTcF prolongation. No apparent dose dependent categorical changes in QTc and brexpiprazole dose was observed.

Mechanism of Action

Brexpiprazole binds with high affinity to multiple serotonin, dopamine and noradrenergic receptors.

While the precise mechanism of action of brexpiprazole in treating psychiatric conditions is unknown, 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 $\alpha_{1B/2C}$ with affinity in the same sub-nanomolar Ki range (Ki: 0,2-0,6 nM). The 5 HT_{1A}/D_2 receptor partial agonist activity in combination with 5-HT_{2A} and $\alpha_{1B/2C}$ receptors antagonism of brexpiprazole may contribute with antipsychotic and antidepressant efficacy.

Clinical efficacy and safety

Schizophrenia

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 2,690 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 6). In the same trial the active reference, quetiapine XR added for assay sensitivity only, separated from placebo.

Table 6: 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 7).

Table 7: Key secondary efficacy results for 6-week trials in schizophrenia

Trial	Treatment group	n	Primary 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)	0,012
	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	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.

5.2 Pharmacokinetic properties

Absorption

Brexpiprazole is well 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 10-12 days of dosing.

Brexpiprazole can be administered with or without food Administration of a 4 mg brexpiprazole tablet with a standard high fat meal did not significantly affect the Cmax or AUC of brexpiprazole. (See section 4.2).

After single and multiple once daily dose administration, brexpiprazole exposure (Cmax and AUC) increased in proportion to the dose administered. In vitro studies of brexpiprazole do not indicate that brexpiprazole is a substrate of efflux transporters such as Multi Drug Resistance Inhibitor (MDRI) P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (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 in vivo is not affected by warfarin, diazepam, and digitoxin.

Biotransformation

Based on in vitro metabolism studies 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.

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 for the other tested transporters.

In vivo brexpiprazole is metabolized 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.

Based on the results of in vitro data, brexpiprazole showed little or no inhibition of CYP450 isoenzymes.

Elimination

Following a single oral dose of [^{14}C]-labeled 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 oral 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.

Special patient populations

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 maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

In patients 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. (see section 4.4 and section 4.2).

Renal Impairment

Patients with impaired renal function (CLcr < 60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function; therefore, the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

In patients with severe renal impairment (CLcr < 30 mL/min), AUC of oral brexpiprazole (2 mg single dose) compared to matched healthy subjects was increased by 68 % while its Cmax was not changed. (see Warnings and Special Precautions; and Dosage and Directions for use).

Age/Gender

After single dose administration of brexpiprazole (2 mg), elderly subjects (older than 65 years old) exhibited similar brexpiprazole systemic exposure (Cmax and AUC) in comparison with the adult subjects (18-45 years old) and female subjects exhibited approximately 40-50 % higher brexpiprazole systemic exposure (Cmax and AUC) in comparison to the male subjects.

Population pharmacokinetic evaluation identified age and female sex as statistically significant covariates affecting brexpiprazole PK, but the effects of PK were not considered clinically relevant.

CYP2D6 Poor Metabolisers

Approximately 8 % of white- and 3–8 % of blacks/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). Population pharmacokinetic evaluation shows that CYP2D6 PMs have 47 % higher exposure to brexpiprazole compared to EMs.

Smoking

Based on studies utilizing human liver enzymes in vitro, brexpiprazole is not a substrate for CYP1A2.

Smoking should, therefore, not have an effect on the pharmacokinetics of brexpiprazole.

5.3 Preclinical safety data

5.3.1 Carcinogenicity, mutagenesis, and impairment of fertility

The lifetime carcinogenic potential of brexpiprazole was evaluated in a two-year study in ICR mice and Sprague-Dawley rats. Brexpiprazole was administered orally (gavage) for two years to mice at doses of 0,75, 2 and 5 mg/kg/day.

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.

These tumours are considered prolactin-mediated and are also observed in rodents with other antipsychotics. Their clinical relevance is unknown.

Brexpiprazole was administered orally (gavage) for two years to rats at doses of 1, 3 and 10 mg/kg/day in male rats or 3, 10 and 30 mg/kg/day in female rats. Long-term administration of brexpiprazole to rats did not induce neoplastic lesions.

Brexpiprazole did not show genotoxic potential in both *in vitro* and *in vivo* studies at clinically relevant exposures.

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 (see section 4.6).

5.3.2 Teratogenic effects

Brexpiprazole was not teratogenic and did not cause adverse developmental effects in rats (at doses up to 30 mg/kg/day).

In a rabbit embryo-foetal development study (at 150 mg/kg/day, a dose that induced maternal toxicity), decreased body weight, retarded ossification, and increased incidences of visceral and skeletal variations were observed in foetuses.

5.3.3 Cardiovascular Toxicity

Decreased blood pressure and prolonged QT interval and QTc were noted in the conscious dog in the safety pharmacology study in the 13-week repeat-dose toxicity study with monkeys and in the juvenile toxicity study with dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: corn starch, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, magnesium stearate.

Tablet coating: hypromellose, talc, titanium dioxide, ferric oxide yellow (0,5 mg; 1 mg and 2 mg tablets), ferric oxide red (0,5 mg and 3 mg tablets), ferrosoferric oxide (2 mg and 3 mg tablets).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store at or below 30 °C

6.5 Nature and contents of container

REXULTI 0,5 mg, 1 mg, 2 mg, 3 mg and 4 mg film-coated tablets are presented in clear and colourless PVC/aluminium foil blister packaging.

The blister cards are packed in an outer cardboard carton containing 28 tablets.

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

H. Lundbeck (Pty) Ltd

Unit 9 Blueberry Office Park

Apple Street Randpark Ridge Ext 114

2156

South Africa

8 REGISTRATION NUMBERS

Rexulti 0,5 mg Film-coated Tablets	51/2.6.5/0501
Rexulti 1 mg Film-coated Tablets	51/2.6.5/0502
Rexulti 2 mg Film-coated Tablets	51/2.6.5/0503
Rexulti 3 mg Film-coated Tablets	51/2.6.5/0504
Rexulti 4 mg Film-coated Tablets	51/2.6.5/0505

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 March 2021

10 DATE OF REVISION OF THE TEXT