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Summary Basis of Decision - Rexulti - Health Canada

From Health Canada

Summary Basis of Decision (SBD) for REXULTI

Contact:

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Summary basis of decision (SBD) documents provide information related to the original authorization of a product. The SBD for Rexulti is located below.

▼ Recent activity

SBDs written for eligible drugs approved after September 1, 2012 will be updated to include post-authorization information. This information will be compiled in a Post-Authorization Activity Table (PAAT). The PAAT will include brief summaries of activities such as submissions for new uses of the product, and whether Health Canada's decision was negative or positive. PAATs will be updated regularly with post-authorization activity throughout the product's life cycle.

▼ Post-Authorization Activity Table (PAAT) for Rexulti

Updated:

2018-05-09

The following table describes post-authorization activity for Rexulti, a product which contains the medicinal ingredient brexpiprazole. For more information on the type of information found in PAATs, please refer to the Frequently Asked Questions: Summary Basis of Decision (SBD) Project: Phase II and to the list of abbreviations that are found in PAATs.

For additional information about the drug submission process, refer to the Management of Drug Submissions Guidance.

Drug Identification Numbers (DINs):

DIN 02461749 - 0.25 mg, brexpiprazole, tablet, oral
DIN 02461757 - 0.5 mg, brexpiprazole, tablet, oral
DIN 02461765 - 1 mg, brexpiprazole, tablet, oral
DIN 02461773 - 2 mg, brexpiprazole, tablet, oral
DIN 02461781 - 3 mg, brexpiprazole, tablet, oral
DIN 02461803 - 4 mg, brexpiprazole, tablet, oral

Post-Authorization Activity Table (PAAT)

Filter items Showing 1 to 2 of 2 entries

Activity/submission type, control number	Date submitted	Decision and date	Summary of activities
Drug product (DINs 02461749, 02491757, 02461765, 02461773, 02461781, 02461803) market notification	Not applicable	Date of first sale: 2017-04-19	The manufacturer notified Health Canada of the date of first sale pursuant to C.01.014.3 of the Food and Drug Regulations.
NDS # 192684	2016-02-26	Issued NOC 2017-02-16	Notice of Compliance issued for New Drug Submission.

▼ Summary basis of decision for Rexulti

Date SBD issued:

2017-05-12

The following information relates to the original authorization of the new drug submission for Rexulti.

Brexpiprazole
0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets, oral

Drug identification number (DIN):

DIN 02461749 - 0.25 mg tablet
DIN 02461757 - 0.5 mg tablet
DIN 02461765 - 1 mg tablet
DIN 02461773 - 2 mg tablet
DIN 02461781 - 3 mg tablet
DIN 02461803 - 4 mg tablet

Otsuka Pharmaceutical Co., Ltd.

New Drug Submission Control Number: 192684

On February 16, 2017, Health Canada issued a Notice of Compliance to Otsuka Pharmaceutical Co., Ltd. for the drug product Rexulti.

The market authorization was based on quality (chemistry and manufacturing), non-clinical (pharmacology and toxicology), and clinical (pharmacology, safety, and efficacy) information submitted. Based on Health Canada's review, the benefit-harm-uncertainty profile of Rexulti is favourable for the treatment of schizophrenia in adults.

▼ 1 What was approved?

Rexulti, an antipsychotic agent, was authorized for the treatment of schizophrenia in adults. In clinical trials, Rexulti was found to significantly improve both positive and negative symptoms of schizophrenia.

Rexulti is not indicated in elderly patients with dementia. The safety and efficacy of Rexulti in patients 65 years of age or older have not been established. Caution should be used when treating geriatric patients.

The safety and efficacy of Rexulti have not been established in patients less than 18 years of age. Rexulti is not indicated in pediatric patients and its use is not recommended in this population.

Rexulti is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

Rexulti was approved for use under the conditions stated in the Rexulti Product Monograph taking into consideration the potential risks associated with the administration of this drug product.

Rexulti (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg brexpiprazole) is presented as a tablet. In addition to the medicinal ingredient, the tablet contains lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, titanium dioxide, ferric oxide yellow (0.25 mg, 0.5 mg, 1 mg, 2 mg tablets), ferric oxide red (0.25 mg, 0.5 mg, 3 mg tablets), and ferrosoferric oxide (0.25 mg, 2 mg, 3 mg tablets).

For more information, refer to the Clinical, Non-clinical, and Quality (Chemistry and Manufacturing) Basis for Decision sections.

Additional information may be found in the Rexulti Product Monograph, approved by Health Canada and available through the Drug Product Database.

▼ 2 Why was Rexulti approved?

Health Canada considers that the benefit-harm-uncertainty profile of Rexulti is favourable for the treatment of schizophrenia in adults.

Schizophrenia is a severe neurodevelopmental brain disorder with a chronic course and typical onset in early adulthood. In accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), diagnostic criteria for schizophrenia include the presence of at least two of the core symptoms of schizophrenia: delusions, hallucinations, disorganized speech, grossly disorganized or abnormal motor behaviour (including catatonia), and negative symptoms (diminished emotional expression, avolition, anhedonia, asociality). In addition, the symptoms must persist for at least 6 months, including at least one month of active-phase symptoms, and they must have a significant impact on the patient's social and occupational functioning (e.g., work, interpersonal relations, self-care) over a significant portion of the time since their onset.

Drugs approved for the treatment of schizophrenia include older drugs known as traditional, first-generation or typical antipsychotics, and more recently approved atypical antipsychotics, also referred to as second-generation antipsychotics. The common mechanism of action of the antipsychotic drugs involves antagonism at dopamine-2 (D_2) receptors, which is also believed to be the mechanism for developing adverse effects including extrapyramidal symptoms and hyperprolactinemia. Typical antipsychotics such as haloperidol and chlorpromazine are associated with frequent extrapyramidal symptoms and tardive dyskinesia, as well as hyperprolactinemia. Atypical antipsychotics may exert antagonism at serotonin (5-hydroxytryptamine) type 2 (5-HT_2) and other receptors, in addition to D_2 receptors, and are less likely to induce extrapyramidal symptoms and hyperprolactinemia at therapeutic doses. However, the atypical antipsychotics may be associated at different extent, depending on the particular drug, with other adverse effects such as weight gain, hyperglycemia and diabetes mellitus, hyperlipidemia, and QTc interval prolongation. The following atypical antipsychotics are approved in Canada for the treatment of schizophrenia in adults: clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine and lurasidone. Aripiprazole (Abilify) differs from the other drugs in the class as its main activity is partial agonism (instead of antagonism) at D_2 receptors.

Brexpiprazole, the medicinal ingredient in Rexulti, is a new chemical entity with partial agonist activity at the 5-HT_{1A}, D_2, and D_3 receptors, and has antagonist activity at the 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α-adrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. The mechanism of action of Rexulti in treating schizophrenia is not established, but it is believed to involve a combination of partial agonist activity at 5-HT_{1A} and D_2 receptors, and antagonist activity at 5-HT_{2A} receptors.

Rexulti has been shown to be efficacious in adult patients with schizophrenia. The market authorization was based on two short-term, randomized, double-blind, placebo-controlled, fixed-dose clinical studies (Studies 230 and 231) in patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia and were experiencing an acute exacerbation of psychotic symptoms. In both studies, the primary efficacy outcome was the mean change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score. The key secondary efficacy outcome was the mean change from baseline to Week 6 in the Clinical Global Impression-Severity (CGI-S) score. In both studies, the 4 mg/day dose of Rexulti showed a significant improvement in the primary efficacy outcome as compared to placebo, whereas the 2 mg/day dose of Rexulti was more effective than placebo only in Study 231.

Supportive data for efficacy of Rexulti in adults with schizophrenia were derived from one longer-term, randomized-withdrawal, placebo-controlled study (Study 232). In addition, the efficacy of Rexulti was also evaluated in a short-term, randomized, double-blind, placebo-controlled and active-reference, flexible-dose clinical study (Study 14644A).

The safety profile of Rexulti in patients with schizophrenia was comparable to that of an atypical antipsychotic drug. Common treatment-emergent adverse events reported in the short-term, fixed-dose trials included gastrointestinal disorders (dyspepsia, dry mouth, diarrhea and abdominal pain), akathisia, tremor, sedation and dizziness. Rexulti was associated with orthostatic hypotension, weight gain, increased triglycerides, extrapyramidal symptoms including akathisia, and prolactin elevations.

Brexpiprazole caused a statistically significant, concentration-dependent suppression of hERG currents *in vitro*. In the dedicated QT/QTc study, Rexulti showed prolongation of the QTcI interval at the therapeutic dose (4 mg, the maximum recommended dose; number of patients, n = 62), but not at the supratherapeutic dose (12 mg, n = 53). No exposure-response relationship was apparent.

The identified safety concerns (including those associated with the atypical antipsychotics class) are addressed in the Warnings and Precautions section of the Rexulti Product Monograph. Furthermore, a Serious Warnings and Precautions box highlights the increased risk of death in elderly patients with dementia who are treated with atypical antipsychotic drugs and emphasizes that Rexulti is not approved for the treatment of patients with dementia.

A Risk Management Plan (RMP) for Rexulti was submitted by Otsuka Pharmaceutical Co., Ltd. to Health Canada. Upon review, the RMP was considered to be acceptable. The RMP is designed to describe known and potential safety issues, to present the monitoring scheme and when needed, to describe measures that will be put in place to minimize risks associated with the product.

A Look-alike Sound-alike brand name assessment was performed and the proposed name Rexulti was accepted.

Overall, the therapeutic benefits of Rexulti in schizophrenia are considered to outweigh the potential risks. Rexulti has an acceptable benefit-harm-uncertainty profile based on the non-clinical data and clinical studies. The identified safety issues can be managed through labelling and adequate monitoring. Appropriate warnings and precautions are in place in the Rexulti Product Monograph to address the identified safety concerns.

This New Drug Submission complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance pursuant to section C.08.004 of the Food and Drug Regulations. For more information, refer to the Clinical, Non-clinical, and Quality (Chemistry and Manufacturing) Basis for Decision sections.

▼ 3 What steps led to the approval of Rexulti?

Submission Milestones: Rexulti

Submission milestone	**Date**
Pre-submission meeting:	2015-10-14
Submission filed:	2016-02-26
Screening	
Screening Acceptance Letter issued:	2016-04-22
Review	
Quality Evaluation complete:	2017-02-08
Clinical Evaluation complete:	2017-02-15
Review of Risk Management Plan complete:	2017-02-15

Submission milestone	Date
Labelling Review complete (including Look-alike Sound-alike brand name assessment):	2017-02-15
Notice of Compliance issued by Director General, Therapeutic Products Directorate:	2017-02-16

The Canadian regulatory decision on the non-clinical and clinical review of Rexulti was based on a critical assessment of the Canadian data package. The foreign review completed by the United States Food and Drug Administration (FDA) was used as an added reference.

For additional information about the drug submission process, refer to the Management of Drug Submissions Guidance.

▼ 4 What follow-up measures will the company take?

Requirements for post-market commitments are outlined in the Food and Drugs Act and Regulations.

▼ 5 What post-authorization activity has taken place for Rexulti?

Summary Basis of Decision documents (SBDs) for eligible drugs authorized after September 1, 2012 will include post-authorization information in a table format. The Post-Authorization Activity Table (PAAT) will include brief summaries of activities such as submissions for new uses of the product, and whether Health Canada's decision was negative or positive. The PAAT will continue to be updated during the product's life cycle.

The PAAT for Rexulti is found above.

For the latest advisories, warnings and recalls for marketed products, see MedEffect Canada.

▼ 6 What other information is available about drugs?

Up to date information on drug products can be found at the following links:

- See MedEffect Canada for the latest advisories, warnings and recalls for marketed products.

- See the Notice of Compliance (NOC) Database for a listing of the authorization dates for all drugs that have been issued an NOC since 1994.
- See the Drug Product Database (DPD) for the most recent Product Monograph. The DPD contains product-specific information on drugs that have been approved for use in Canada.
- See the Notice of Compliance with Conditions (NOC/c)-related documents for the latest fact sheets and notices for products which were issued an NOC under the Notice of Compliance with Conditions (NOC/c) Guidance Document, if applicable. Clicking on a product name links to (as applicable) the Fact Sheet, Qualifying Notice, and Dear Health Care Professional Letter.
- See the Patent Register for patents associated with medicinal ingredients, if applicable.
- See the Register of Innovative Drugs for a list of drugs that are eligible for data protection under C.08.004.1 of the Food and Drug Regulations, if applicable.

▼ 7 What was the scientific rationale for Health Canada's decision?

▼ 7.1 Clinical basis for decision

Clinical Pharmacology

The mechanism of action of brexpiprazole, the medicinal ingredient in Rexulti, in treating schizophrenia is unknown. The efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at the serotonin (5-hydroxytryptamine) type 1A (5-HT_{1A}) receptors and at dopamine-2 (D_2) receptors with antagonist activity at serotonin 5-HT_{2A} receptors. The clinical relevance of these receptor interactions with brexpiprazole is unknown.

The clinical pharmacology included reports on the human pharmacodynamic and pharmacokinetic studies. The clinical pharmacological data support the use of Rexulti for the recommended indication.

For further details, please refer to the Rexulti Product Monograph, approved by Health Canada and available through the Drug Product Database.

Clinical Efficacy

The efficacy of Rexulti in the treatment of adults with schizophrenia was evaluated in two short-term, randomized, double-blind, placebo-controlled, fixed-dose clinical studies (Studies 230 and 231) and one longer-term, randomized-withdrawal,

placebo-controlled study (Study 232). In addition, the efficacy of Rexulti was also evaluated in a short-term, randomized, double-blind, placebo-controlled and active-reference, flexible-dose clinical study (Study 14644A).

Studies 230 and 231 were Phase III, 6-week, multicentre, randomized, double-blind studies to assess the efficacy, safety, and tolerability of each of three fixed doses of Rexulti (0.25 mg or 1 mg, 2 mg, and 4 mg) versus placebo for the inpatient treatment of adults with an acute exacerbation of schizophrenia who would benefit from hospitalization or continued hospitalization for the acute exacerbation. The acute exacerbation of schizophrenia was determined by the diagnostic criteria set by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.), and a score ≥40 on the Brief Psychiatric Rating Scale (BPRS), with a score ≥4 on two or more of specific BPRS items (hallucinatory behaviour, unusual thought content, conceptual disorganization, suspiciousness), and a Clinical Global Impression-Severity (CGI-S) score ≥4.

Study 14644A was a Phase III, 6-week, multicentre, randomized, double-blind, placebo-controlled and active-reference study to assess the efficacy, safety, and tolerability of flexible-dose Rexulti (2 mg/day to 4 mg/day) versus placebo in adult inpatients with an acute exacerbation of schizophrenia who were willing to be hospitalized until the completion/withdrawal visit. The active-reference drug used in the study was quetiapine extended release (at a dose of 400 mg/day to 800 mg/day). The patient inclusion/exclusion criteria were similar to those used in the fixed-dose studies.

In all three placebo-controlled studies, the primary efficacy outcome was the mean change from baseline to Week 6 in the PANSS total score. The key secondary efficacy outcome was the mean change from baseline to Week 6 in the CGI-S score.

Studies 230 and 231 demonstrated the efficacy of Rexulti in comparison with placebo. In both studies, the 4 mg/day dose of Rexulti showed a significant improvement for the primary efficacy outcome as compared to placebo, whereas the 2 mg/day dose of Rexulti was more effective than placebo only in Study 231.

In Study 14644A, the treatment with Rexulti did not show superiority over placebo. However, the active reference confirmed the assay sensitivity of the study.

Study 232 was a Phase III, multicentre, randomized-withdrawal, double-blind, placebo-controlled trial in adult patients with schizophrenia who were diagnosed in accordance with the DSM-IV-TR criteria and had a history of the illness for at least three years prior to screening. Also, the patients were experiencing an exacerbation of psychotic symptoms as demonstrated by a PANSS total score >80 at screening, met the criteria for stability for at least 12 weeks during single-blind treatment with Rexulti (at flexible doses of 1 mg/day to 4 mg/day for up to 36 weeks), and were

randomized to continue on Rexulti dose at stabilization or to switch to placebo, for up to 52 weeks for observation of relapse. Stability criteria during the open-label treatment included a PANSS total score ≤70, with a score of ≤4 (moderate or less severe) on each of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behavior and unusual thought content; a CGI-S score ≤4 (moderately ill); no current suicidal or aggressive behavior; and a stable dose for at least the last 4 weeks of the stability period. Relapse was defined as meeting at least one of the following 4 criteria: at least a minimal worsening in the Clinical Global Impression-Improvement (CGI-I) score and at least moderately severe score in the 4 items of the PANSS scale described above; hospitalization due to worsening of schizophrenia; current suicidal behavior; or aggressive behavior resulting in clinically significant injury to self or others, or property damage. The primary efficacy endpoint was the time to exacerbation of psychotic symptoms/impending relapse. The key secondary efficacy endpoint was the percentage of patients with exacerbation of psychotic symptoms/impending relapse.

A pre-specified interim analysis, conducted after 50% of the events planned in the calculation of power (45 impending relapse events), demonstrated a statistically significantly longer time to relapse in patients randomized to the Rexulti group compared to placebo-treated patients. The trial was subsequently terminated early because of demonstrated efficacy. The time to impending relapse was significantly delayed with Rexulti as compared to placebo in both the interim and final analyses. Furthermore, the impending relapse rates were significantly lower in the Rexulti group compared to placebo in both the interim analysis (15% vs. 37%) and final analysis (13.5% vs. 38.5%).

Notably, in the evaluation of provided clinical data for other drugs approved in the atypical antipsychotics class, placebo-controlled, randomized-withdrawal trials similar to Study 232 have not been considered by Health Canada as supportive of an indication for maintenance treatment. Namely, schizophrenia is a chronic disorder, and in a population enriched with patients who have responded to acute treatment with the studied drug, a conversion to placebo treatment increases the risk of relapse and likely results in significant separation between the drug and placebo, without demonstrating how the drug actually performs in long-term treatment. In addition, many of these studies are terminated following an interim analysis of efficacy, which further limits the drug exposure and collection of long-term data. Such studies were, however, considered by Health Canada as supportive of acute treatment efficacy (i.e., the increased risk of relapse after switching to placebo can be interpreted as a demonstration of a true drug effect during the acute open-label treatment). Therefore, Study 232 is considered as supportive of the clinical efficacy of Rexulti because the continuation of the treatment with Rexulti delayed relapses in an enriched patient

population who responded to open-label acute treatment with Rexulti, as compared to the patients who switched to placebo. However, the study is not considered supportive of an indication for maintenance treatment of schizophrenia.

Indication

The original New Drug Submission (NDS) for Rexulti was filed with the following proposed indication:

> Rexulti is indicated for treatment of schizophrenia.
> The efficacy of Rexulti was established in two 6-week controlled studies and one long-term maintenance study (52 weeks) in adult subjects with schizophrenia. In clinical trials, Rexulti was found to significantly improve both positive and negative symptoms, and significantly delayed time to impending relapse.

As for studies of similar design submitted to Health Canada for other approved drugs in the atypical antipsychotics class, the aforementioned long-term maintenance study in adult subjects with schizophrenia (Study 232) was not considered supportive of an indication for maintenance treatment of schizophrenia. Accordingly, Health Canada approved the following indication:

> Rexulti (brexpiprazole) is indicated for treatment of schizophrenia in adults.
> In clinical trials, Rexulti was found to significantly improve both positive and negative symptoms.

Clinical Safety

In the clinical drug development program, a total of 2,579 patients with schizophrenia were exposed to at least one dose of Rexulti. Of those, 840 patients were exposed to Rexulti for at least 26 weeks, and 492 patients for 52 weeks or longer.

Serious treatment-emergent adverse events and treatment-emergent adverse events leading to discontinuation of treatment were mostly related to worsening of schizophrenia. Other treatment-emergent adverse events leading to discontinuation infrequently included increased hepatic enzymes, akathisia, somnolence, increased weight, increased blood creatinine phosphokinase, rhabdomyolysis, and tremor.

Common treatment-emergent adverse events reported in the short-term, fixed-dose trials included gastrointestinal disorders (dyspepsia, dry mouth, diarrhea and abdominal pain), akathisia, tremor, sedation and dizziness.

Overall, the safety profile of Rexulti in patients with schizophrenia was as expected for an atypical antipsychotic drug. The treatment with Rexulti was associated with orthostatic hypotension, weight gain, increased triglycerides, extrapyramidal symptoms including akathisia, and prolactin elevations.

Rexulti is predominantly metabolized by cytochrome P450 (CYP)3A4 and CYP2D6 enzymes. Drug interactions have the potential to increase exposure to Rexulti and dose adjustments are necessary to avoid dose-dependent adverse reactions. Accordingly, the Rexulti Product Monograph includes recommendations for dosage adjustments in special populations (patients with hepatic and renal impairment, elderly patients), patients who are known CYP2D6 poor metabolizers and patients taking concomitant CYP3A4 inhibitors, CYP2D6 inhibitors, or strong CYP3A4 inducers.

The Phase II/III trials in schizophrenia did not include a sufficient number of elderly patients to evaluate safety comparatively to younger adults (there were five patients aged 65 years and over in the short-term trials, and one patient in the open-label trials). However, given the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant diseases or other drug therapy in the elderly, the Rexulti Product Monograph recommends a cautious dose selection for an elderly patient, usually starting at the low end of the dosing range. Furthermore, the Serious Warnings and Precautions box in the Rexulti Product Monograph highlights the increased risk of death in elderly patients with dementia who are treated with atypical antipsychotic drugs and emphasizes that Rexulti is not approved for the treatment of patients with dementia.

In a multicentre, randomized, double-blind, placebo- and positive-controlled, parallel-group, multiple-dose electrocardiogram (ECG) assessment study, patients with schizophrenia or schizoaffective disorder received treatment with Rexulti at a therapeutic dose of 4 mg/day (number of patients, n = 62) or a supratherapeutic dose of 12 mg/day (n = 53) for 11 days. On Day 11, the maximum mean difference from placebo-adjusted mean change from baseline in the QTcI interval was 8.3 ms (90% confidence interval [CI]: 3.7, 12.9) at 6 hours post-dosing in the Rexulti 4 mg/day group and 3.1 ms (90% CI: -1.7, 8.0) at 4 hours post-dosing in the Rexulti 12 mg/day group. No exposure-response relationship was apparent. Subgroup analyses suggested that the QTc interval prolongation was larger in female subjects than in males. Limitations of the gender subgroup analyses included diminished statistical power, especially in the small female subgroup. A summary of the study results and recommendations relevant for QTc-prolonging drugs were included in the Warnings and Precautions section of the Rexulti Product Monograph.

Appropriate warnings and precautions are in place in the approved Rexulti Product Monograph to address the identified safety concerns.

For more information, refer to the Rexulti Product Monograph, approved by Health Canada and available through the Drug Product Database.

▼ 7.2 Non-clinical basis for decision

Brexpiprazole, the medicinal ingredient in Rexulti, is a new active substance with a similar chemical structure to the antipsychotic drug aripiprazole (Abilify). An acceptable non-clinical program was conducted with brexpiprazole in support of its use in human clinical trials, including non-clinical, safety pharmacology, and toxicology studies.

Pharmacokinetic studies conducted in rats, rabbits, dogs, and monkeys, as well as *in vitro* studies with human tissue demonstrated similar biotransformation pathways across species including humans. Ten common metabolites were identified, with major metabolites generated predominantly by cytochrome P450 (CYP) isoforms CYP3A4 and CYP2D6, as well as by flavin-containing monooxygenase 3 (FMO3). Brexpiprazole and its main metabolite are not expected to inhibit CYP-mediated metabolism and were not found to be substrates of various membrane-bound transporters at therapeutic doses.

In safety pharmacology studies, brexpiprazole induced significant central nervous system depression at doses >24-fold the maximum recommended human dose (MRHD of 2.46 mg/m^2 body surface area based on 4 mg/day brexpiprazole for a 60 kg patient). In conscious telemetry dogs, a single oral dose of 10 mg/kg, and 30 mg/kg caused significant QT prolongation at 81- to 243-fold MRHD. Repeated dose toxicity studies with administration periods of 4 to 39 weeks were conducted at oral doses from 1 to 30 mg/kg/day in monkeys and juvenile dogs and up to 100 mg/kg/day in rats (5- to 244-fold MRHD). Clinical signs of central nervous system depression, hypoactivity and tremor were observed in all animal species, which generally decreased over time at low doses but persisted at higher doses. Significant QT prolongation intervals were mostly observed on Day 1 of administration at doses >3 mg/kg in dogs and monkeys. At high doses (≥30 mg/kg), lower respiration rates, and decreases in body temperature and blood pressure were observed throughout the period of administration. At the lowest doses tested, female rodents had an increased body weight compared with the control group at the end of the studies. In juvenile male rats, a decrease in body weight, pubertal delays, and feminization of the mammary glands were noted at the end of the administration period at doses ≥10 mg/kg compared with the control group. An increase in the incidence and/or severity of immature male genitalia was observed in the 30 mg/kg group in juvenile dogs. Hematology and urinalysis findings were mostly unremarkable at low doses, whereas at high doses of brexpiprazole, a decrease in white blood cells counts as well as an increase in blood cholesterol and phospholipids were commonly reported in most species.

Reproductive and developmental toxicity studies with brexpiprazole conducted in rats established a low safety margin for female fertility at 0.3 mg/kg (0.7-fold MRHD) and embryo viability at 3 mg/kg (7-fold the MRHD). Brexpiprazole was not found to have a significant carcinogenic potential in mouse (6-fold MRHD) and rat (73-fold MRHD in females) in lifetime studies, with the exception of mammary tumors specifically

observed in female mice at ≥1-fold MRHD. Brexpiprazole was not mutagenic *in vivo* in rats based on the micronucleus assay and the unscheduled deoxyribonucleic acid (DNA) synthesis assay up to 2000 mg/kg. A genotoxic potential for brexpiprazole was observed *in vitro* in the forward gene mutation assay in mouse lymphoma cells and in chromosomal aberration assay in Chinese hamster ovary cells at cytotoxic concentrations of 50-70 µM (i.e.,>100-fold MRHD), but not in the bacterial reverse mutation assay. Brexpiprazole has the potency to increase serum prolactin levels in both male and female rats, although the expected levels at therapeutic doses were not determined in animals. Results of physical dependence studies with brexpiprazole were negative with respect to withdrawal symptoms in rats or reinforcing effects in monkeys.

The results of the non-clinical studies as well as the potential risks to humans have been included in the Rexulti Product Monograph. In view of the intended use of Rexulti, there are no pharmacological/toxicological issues within this submission which preclude authorization of the product.

For more information, refer to the Rexulti Product Monograph, approved by Health Canada and available through the Drug Product Database.

▼ 7.3 Quality basis for decision

The Chemistry and Manufacturing information submitted for Rexulti has demonstrated that the drug substance and drug product can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted, and adequate controls are in place for the commercial processes. Changes to the manufacturing process and formulation made throughout the pharmaceutical development are considered acceptable upon review. Based on the stability data submitted, the proposed shelf life of 36 months is acceptable when the drug product is stored between 15°C and 30°C.

Proposed limits of drug-related impurities are considered adequately qualified, i.e., within International Council for Harmonisation (ICH) limits and/or qualified from toxicological studies.

All sites involved in production are compliant with Good Manufacturing Practices.

All non-medicinal ingredients (excipients) found in the drug product are acceptable for use in drugs according to the Food and Drug Regulations.

The excipient lactose monohydrate is derived from milk for human consumption, which is unlikely to present any risk of contamination with transmissible spongiform encephalopathy (TSE) agents.

Date modified:

2016-10-13

Government of Canada activities and initiatives

#YourBudget2018 – Advancement

Advancing our shared values

#YourBudget2018 – Reconciliation

Advancing reconciliation with Indigenous Peoples

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