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Full Title
Brexpiprazole CH RMP Summary

Report Number/Short Title
Brexpiprazole CH RMP Summary

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Summary of the Risk Management Plan (RMP)

Rexulti® (brexpiprazole)

0.5 mg, 1 mg, 2 mg, 3mg, 4 mg

Film-coated tablets

RMP Version 1.0
Document date: 27 August 2018
Marketing authorisation holder: Lundbeck (Schweiz) AG

Summary of the Risk Management Plan (RMP)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate the risks potentially associated with the use of medicine, as well as to prevent or minimise them.

The RMP summary of £Rexulti® includes essential safety information and risks that might be associated with use of the product and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Rexulti® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Lundbeck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Rexulti®.

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	Extrapyramidal symptoms (EPS)
Important potential risks	Seizure Suicidality Dyslipidaemia
Missing information	Use in pregnancy and lactation Use in paediatrics Use in elderly (age >65) Use in patients with hepatic impairment Use in patients with renal impairment Psychiatric comorbidities: include generalized anxiety disorder, panic disorder, obsessive compulsive disorder (OCD) and social phobia Patients with chronic medical illnesses (clinically significant or uncontrolled medical illness) Substance abuse Insulin Dependent Diabetes Mellitus (IDDM)

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
None	NA	NA	NA	NA

VI.1.3 Summary of Post authorisation efficacy development plan

Copy table IV.3 from Part IV

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status	Date for submission of interim or final reports
None	NA	NA		NA

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Extrapyramidal Symptoms	"Undesirable Effects" in the SPC	None
Seizure	"Warnings and Precautions" section; advice to the patient in the PIL	None
Suicidality	"Warnings and Precautions" section in the SPC; warning text in the PIL	None
Dyslipidaemia	"Warnings and Precautions" section in the SPC; advice to the patient in the PIL	None
Use in pregnancy and lactation	Sections "Pregnancy/ Lactation" in the SPC	None
Use in paediatrics	Section "Children and Adolescents" in the SPC	None
Use in elderly (age> 65)	Section "Use in Elderly" in the SPC	None
Use in patients with hepatic impairment	Section "Dosage/ Application", and Section "Hepatic Impairment" in the SPC	None
Use in patients with renal impairment	Section "Dosage/ Application", and Section "Renal Impairment" in the SPC	None
Psychiatric comorbidities: include generalized anxiety disorder, panic disorder, obsessive compulsive disorder (OCD) and social phobia	Routine Pharmacovigilance	None
Patients with chronic medical illnesses (clinically significant or uncontrolled medical illness)	"Warnings and Precautions" Section in the SPC	None
Substance abuse	Routine Pharmacovigilance	None
Insulin Dependent Diabetes Mellitus	Section "Hyperglycaemia and	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
(IDDM)	Diabetes Mellitus" in the SPC	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Schizophrenia is a severely debilitating mental illness that affects approximately 1 % of the world population during their life, but there is substantial variability in incidence rates across international epidemiological studies.

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

It is usually diagnosed early in life with first-episode occurrence in adolescents. Most individuals with schizophrenia reach the progressive stage of the disease at 15 to 45 years old.

VI.2.2 Summary of treatment benefits

Clinical development program for Rexulti consisted of 3 short-term pivotal studies and 5 long-term studies with up to one year duration.

A total of 5636 subjects have been treated with brexpiprazole in phase 2 and 3 clinical trials, including 2579 patients suffering from schizophrenia.

Rexulti demonstrated efficacy in 2 out of 3 short-term pivotal studies and maintenance of the effect in one long-term study. Remaining 4 long-term studies were designed to assess safety of Rexulti.

Overall, Rexulti was shown to be efficacious in dose range 2 to 4 mg/day, in short-term treatment and long-term maintenance treatment of adults with schizophrenia, based on assessments of multiple domains of the disease. It reduced symptoms on a standard rating scale called PANSS (positive and negative syndrome scale). The PANSS score, which ranges from a minimum of 30 (no symptoms) to a maximum of 210 (severest symptoms), was around 95 at the start of treatment. After 6 weeks, depending on the study and dose, the PANSS score fell by 9 to 20 points with Rexulti compared with 6 to 16 points with placebo.

VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies nearly all patients were aged between 18 and 65, with mean age of subjects across being in range 37 and 41 years. Rexulti worked independently of patients' age, gender, race and BMI. There is no evidence to suggest that results would be any different in patients older than 65 years. Clinical studies in patients under age of 18 are ongoing.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Extrapyramidal symptoms	Uncontrolled twitching or	Gradual increase in dose

Risk	What is known	Preventability
	jerking, a constant urge to move, shaking	following treatment initiation, according to the SPC; regular assessment of patient's response and tolerability

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Seizure (fits or epilepsy)	Patients treated with Rexulti may be at an increased risk of developing seizures. There are theoretical mechanisms as seizures have been seen with other medicines from the same class

Missing information

Risk	What is known
Limited information on use in pregnancy and lactation	Rexulti was not tested in pregnant or lactating women.
Use in paediatrics	Rexulti was not tested in patients younger than 18 years; clinical studies in adolescents and children are ongoing.
Use in elderly (age> 65)	Rexulti was not tested in elderly patients suffering from schizophrenia. However, it was tested in elderly patients with other brain disorders and it was shown to be safe and well tolerated
Limited information on use in patients with liver impairment	Rexulti was tested in a small number of patients with decreased liver function and it was safe and well tolerated
Limited information on use in patients with kidney impairment	Rexulti was tested in small number of patients with decreased kidney function and it was safe and well tolerated
Limited information in patients with other co-existing mental disorders, such as generalized anxiety disorder, panic disorder, obsessive compulsive disorder (OCD) and social phobia	Rexulti was investigated in other indications, such as major depression and it was safe and well tolerated. Limited number of patients with other mental disorders was included in clinical trials with Rexulti. There is no reason to believe that safety profile of Rexulti will be different in these patients.
Limited information in patients with co-existing medical illnesses (clinically significant or uncontrolled medical illness)	Limited number of patients with co-existing medical illnesses was included in clinical trials with Rexulti. In this small group of patients Rexulti was well tolerated.
Lack of information in patients with substance abuse	Patients with significant substance abuse were excluded from clinical trials with Rexulti.
Limited information in patients with Insulin Dependent Diabetes Mellitus (IDDM)	Limited number of patients with IDDM was included in clinical trials with Rexulti. Rexulti was well tolerated in this small group of patients.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Swiss Product Information for Rexulti® can be found at www.swissmedicinfo.ch.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
None	NA	NA	NA	NA

Studies which are a condition of the marketing authorisation

NA

VI.2.7 Summary of changes to the Risk Management Plan over time

This is initial Risk Management Plan for Rexulti submitted in Switzerland.

Table 1. Major changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
	At time of authorisation dd/mm/yyyy	Identified Risks Potential Risks Missing information	
<E.g. 7.0>	<E.g. 17/08/2012>	<E.g. Allergic conditions added as an identified risk Hypersensitivity removed as an identified risk Severe infection added as an identified risk Convulsions added as a potential risk>	<E.g. The previous term hypersensitivity was updated to allergic conditions to include angioedema and urticarial>