Summary of Risk Management Plan (RMP)

Zinbryta® (Daclizumab beta)

Biogen Switzerland AG

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SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR ZINBRYTA (DACLIZUMAB BETA)

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 and follow the risks as well as to prevent or minimise them.

The RMP summary of Zinbryta is a concise document 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 Zinbryta in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Biogen Switzerland AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zinbryta.

Overview of disease epidemiology

Onset of MS is usually between the ages of 20 and 45 years, and rarely occurs in children or in adults 60 years and older. Approximately twice as many women than men have MS. Approximately 90% of individuals develop RRMS, which is characterised by episodic bouts of neurological worsening separated by periods of relative stability. About half of patients with MS relapses develop progressive MS within 10 to 20 years after diagnosis. The total number of people with MS worldwide is estimated to be 2 to 2.5 million, and approximately 93 of every 100,000 persons in Europe have MS. MS is most common in temperate regions, especially those with large populations of Northern European origin, including the US, Canada, New Zealand, and parts of Australia. MS is less common in tropical areas and Asia.

Summary of treatment benefits

Daclizumab is a monoclonal antibody that is administered once a month as an SC injection. Daclizumab works by stopping the immune system from damaging the brain and spinal cord. It affects MS disease in different ways compared with other currently available MS therapies. This is important because not all patients respond to therapy in the same way, either in terms of disease control or the types of side effects experienced.

Two main studies compared daclizumab with placebo or interferon beta-1a in terms of the ability to improve MS disease. In the first study of 621 patients, daclizumab reduced the rate of MS relapses by 54% and the risk of disability progression by 76% compared with placebo. In the second study of 1,841 patients daclizumab reduced the rate of MS relapses by 45% and delayed disability progression by 27% compared with interferon beta-1a. Interferon beta-1a is a medication given by intramuscular injection, and was used as a comparative treatment because of its beneficial effects on

MS. Daclizumab also reduced the number of MS brain lesions, and the day-to-day impact of MS symptoms, to a greater extent than either placebo or interferon beta-1a.

Unknowns relating to treatment benefits

In main and supporting studies, most subjects were White and between 18 to 55 years of age. There is no evidence that results would be different in non-White or older subjects. Studies have not been performed in subjects under the age of 18 years, in elderly subjects (over the age of 65 years), in subjects with hepatic impairment, in subjects taking concomitant hepatotoxic medications, or in pregnant or lactating women.

Summary of safety concerns

Summary of important identified risks

Risk	What is known	Preventability
Abnormal liver tests and serious liver injury	Serious liver problems have occurred in about 1 in 100 patients. Patients may experience the following symptoms: unexplained nausea (feeling sick to your stomach), vomiting (being sick), stomach pain, increased tiredness, loss of appetite (anorexia), yellowing of the skin or the whites of the eyes, and dark (tea-colored) urine.	Serious liver injury may be prevented through monitoring for early signs symptoms and liver function testing. Doctors will perform monthly blood tests to monitor liver function. If symptoms appear or in the event of elevated liver function tests, they can be treated with standard medical therapies or by discontinuation of Zinbryta. Patients should call a doctor immediately if they have any of these symptoms. They may be a sign of possible liver problems.
Serious skin reactions	About 1 in 3 people treated with Zinbryta have experienced some sort of skin reaction. In about 2 in 100 patients, these reactions were serious enough to require hospitalisation. Skin reactions have included severe rash, and in some cases the rash was widespread.	Skin reactions can be treated with standard medical treatment or by discontinuation of Zinbryta. Patients should contact their doctor if they develop a severe widespread rash.
Infections and serious infections	About 1 in 2 people treated with Zinbryta have experienced some sort of infection. The most common infections were upper respiratory tract infections. The infections were serious in about 4 in 100 patients. The types of infections reported, as well as the course of the infections, were typical of those reported in patients with MS.	Infections and serious infections can be treated with standard medical treatment or by discontinuation of Zinbryta.

Risk	What is known	Preventability
Prolonged diarrhoea ranging from mild to severe, sometimes with fever and abdominal pain (colitis)	Fewer than 1 in 100 patients treated with Zinbryta had colitis serious enough to require hospitalisation. Symptoms included diarrhoea that does not go away, stomach pain, fever, or blood in the stools.	Colitis can be treated with standard medical therapies or by discontinuation of Zinbryta. Patients are instructed to contact their doctor if they experience any of these symptoms.
Depression	Fewer than 1 in 100 patients experienced serious depression. In the majority of patients with serious depression suicide attempt and thoughts of self harm were also reported.	Patients with depression or a history of depression should be closely monitored. They should report immediately to their physician any symptoms of depression or if they have thoughts of self harm. If a patient develops severe depression, and/or suicidal ideation, discontinuation of Zinbryta should be considered
Serious lymphadenopathy (enlarged lymph nodes)	Approximately 1 in 100 patients experienced serious enlarged lymph nodes which required hospitalization, lymph node biopsy and discontinuations of Zinbryta treatment.	In clinical studies, enlarged lymph nodes occurred throughout Zinbryta treatment period. Discontinuation due to lymphadenopathy occurred in fewer than 1 in 100 patients. The majority of patients with enlarged lymph nodes continued on treatment with Zinbryta, and the majority of cases resolved within 3 months.
Autoimmune haemolytic anaemia	Fewer than 1 in 100 patients experienced autoimmune haemolytic anaemia in clinical studies.	All patients recovered after receiving appropriate treatment and discontinuing the drug.

Summary of important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Infections that may occur in individuals with weakened immune systems (opportunistic infections)	Because Zinbryta is an antibody, it affects the body's immune system. Therefore, in theory, Zinbryta could lead to the development of infections that are typically seen in patients with weakened immune systems. However, in clinical studies, the types of infections reported in subjects with MS who received Zinbryta were typical of those seen in MS patients, and were not representative of those infections that are seen in patients with weakened immune systems.
Cancer	Because Zinbryta affects the body's immune system, it might theoretically be associated with the development of cancer. There is no evidence from the clinical studies to indicate that Zinbryta causes

Risk	What is known (Including reason why it is considered a potential risk)
	cancer.
Acute serious hypersensitivity reactions (serious allergic reactions soon after receiving a dose of Zinbryta)	One subject had a potential serious allergic reaction after receiving a dose of daclizumab (fewer than 1 in 1,000 people in the clinical studies have experienced this serious reaction). The reaction was not life threatening. Patients should not use Zinbryta if they have a history of severe allergy to daclizumab or to any of the other ingredients in this medicine. Patients should contact a doctor immediately if they experience difficulty breathing or swelling around the face (lips, tongue, or throat), or rashes (i.e., hives, urticaria).
Prolonged severe lymphopenia (decreased count of type of white blood cells called lymphocytes)	Mild and moderate decreases in lymphocyte count were identified during Zinbryta treatment in clinical studies. Prolonged and severe decrease in lymphocyte count was not observed with Zinbryta however because it is a known risk factor for infections that may occur in individuals with weakened immune systems (opportunistic infections) regular blood count monitoring during Zinbryta treatment is recommended.

Summary of missing information

Risk	What is known
Use of Zinbryta in patients under 18 years of age	Zinbryta has not been studied in patients under the age of 18 years.
Use of Zinbryta in elderly patients (over the age of 65 years) and in patients over 55 years of age	Very small numbers of patients older than 55 participated in clinical studies with Zinbryta. Clinical studies did not include elderly patients (i.e., those over 65 years of age).
Use of Zinbryta during pregnancy	Limited information is available on the effects of Zinbryta in pregnant women.
Use of Zinbryta in lactating women	No information is available on the effects of Zinbryta in lactating women.
Use of Zinbryta in patients with liver function problems	Zinbryta has not been studied in patients with liver function problems.
Use of Zinbryta at the same time as hepatotoxic medications (medications that affect the liver)	Limited information is available on the use of Zinbryta at the same time as medications that cause liver injury.

Summary of risk minimisation measures by safety concern

This medicine has additional risk minimisation measures. These include a Hepatic Risk Management Guide for physicians and a Patient CardThese additional risk minimisation measures are for the following risks:

Serious liver injury

Risk minimisation measures: Hepatic Risk Management Guide, Patient Card
Objective and rationale: To educate patients and physicians about the risk of severe hepatic injury and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. Proposed action: The Hepatic Risk Management Guide will contain information for the physician on the risk of elevations in liver enzyme levels and severe liver injury in patients treated with Zinbryta, as well guide the physician/patient discussion around hepatic risk and the measures to manage this risk. The physician should discuss the risk of hepatic injury with the patient and provide them with a Patient Card. The Card informs patients of the risk of severe hepatic injury, and the possible symptoms, so that they are aware of situations in which they should contact a physician in a timely manner. In addition, the Card explains the need for monitoring of liver function and educates the patient on the importance of adherence to their monthly blood tests The Patient Card is designed to enable the physician to present patient-friendly information about Zinbryta to a patient at the time Zinbryta is prescribed. It will focus on the potential for severe hepatic injury with Zinbryta, and will also include information about symptoms of liver injury and instructions about monthly liver function monitoring.

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
Global paediatric study with 2-year treatment duration followed by 2-year extension	To evaluate the activity, safety/tolerability, and pharmacokinetics (PK) of Zinbryta in patients from 10 to less than 18 years of age	Safety profile in patients under the age of 18 years	Planned	Submission date dependent on study dates. Study finish by August 2019 per the agreed Paediatric Investigation Plan (PIP) (EMEA-001349-PIP01-12-M01; Decision P/0147/2014)
Global Phase 4 pregnancy registry (109MS402)	To prospectively evaluate pregnancy and infant outcomes in pregnant women with MS who were exposed to Zinbryta since the first day of their last menstrual period (LMP) prior to conception or at any time during pregnancy	Effects during pregnancy	Planned	Planned final report: 2028
Epidemiological	To assess the	Transaminase	Planned	Planned final

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
database study	effectiveness of risk minimisation measures	elevations/serious hepatic injury		report: Dependent on dates study is conducted
Central tracking of distribution of physician guide to health care professionals (HCPs) in EEA	To evaluate process indicators of effectiveness of the distribution of physician education materials	Transaminase elevations/serious hepatic injury	Planned	With Periodic Safety Update Reports (PSURs)
Feasibility study of MS registries	To assess the feasibility of conducting Post Authorisation Safety Study using MS registries	To assess whether important potential risks could be studied using MS registries	Planned	Report of feasibility assessment within 6 to 12 months of marketing in the EU

Studies which are a condition of the marketing authorisation

Not applicable.

Summary of changes to the risk management plan over time

Major changes to the risk management plan over time

Not applicable.