Swiss Summary of the Risk Management Plan (RMP)

for

Zinplava®

(Bezlotoxumab 1000mg)

Concentrate for solution for infusion

Version 2.2 (14-Dec-2020)

Marketing Authorisation Holder: MSD Merck Sharp & Dohme AG

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 Zinplava® 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 authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Zinplava® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

MSD Merck Sharp & Dohme AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zinplava®.

1 Elements for Summary Tables in the EPAR

1.1 Summary Table of Safety Concerns

Table 1 Summary of Safety Concerns

Important identified risks	None
Important potential risks	Potential for Immunogenicity Impaired safety in patients with underlying CHF or with history of CHF
Missing information	Exposure in Patients 1 year to <18 years of age

1.2 Table of Ongoing and Planned Studies in the Post-authorisation Pharmacovigilance Development Plan

Table 2 Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)
(MK-6072-P001): Trial in Paediatric Patients Aged 1year to <18 years Catergory 3	Randomised, double-blind, single dose, placebo-controlled trial to evaluate, safety, tolerability, pharmacokinetics, and efficacy of a single infusion of bezlotoxumab (MK-6072, human monoclonal antibody to *Clostridium difficile* toxin B) as add-on to standard of care antibiotic treatment in children from 1 to less than 18 years of age with *Clostridium difficile* infection (CDI).	To determine a dosing recommendation for bezlotoxumab in the paediatric population and provide information on safety and efficacy in patients with CDI who are 1 year to < 18 years of age. In addition, ADA assessments will be conducted to assess the potential for immunogenicity.	Ongoing:	Final Report: Nov 2022

1.3 Summary of Post-authorisation Efficacy Development Plan

Not applicable.

1.4 Summary Table of Risk Minimisation Measures

Table 3 Summary of Safety Concerns and Risk Minimisation Activities

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Potential Risk: Potential for Immunogenicity	**SmPC:** **Section 4.2 Posology and method of administration** *The experience with ZINPLAVA in patients is limited to a single CDI episode and single administration.* **4.4 Special Warnings and precautions for use** *There is no experience with repeat administration of ZINPLAVA in patients with CDI. In clinical trials, patients with CDI were only administered a single dose of ZINPLAVA.* **Section 4.8 Undesirable effects** *Section for Description of selected adverse reactions under Immune-related Adverse Reactions states that in a Phase 1 clinical trial, healthy subjects received two consecutive doses of 10 mg/kg of bezlotoxumab separated by 12 weeks. The adverse reactions after the second dose were not markedly different from those observed after the first dose, and are consistent with adverse reactions observed in the two Phase 3 trials (MODIFY I and MODIFY II) in which all patients received a single dose.* **Section 5.1 Pharmacodynamic properties** *Section 5.1 under Immunogenicity states that immunogenicity of ZINPLAVA was evaluated using an electrochemiluminescence (ECL) assay in MODIFY I and MODIFY II.* *Following treatment with ZINPLAVA in MODIFY I and MODIFY II, none of the 710 evaluable patients tested positive for treatment-emergent anti-bezlotoxumab antibodies. Although ZINPLAVA is intended for single dose administration, the immunogenicity of bezlotoxumab following a second administration of 10 mg/kg, 12 weeks after the first dose, was assessed in 29 healthy subjects. No anti-bezlotoxumab antibodies were detected after the second dose.* *There are no data on repeated administration of bezlotoxumab in patients with CDI.* **Package Leaflet:** Not applicable	None
Important Potential Risk: Impaired safety in patients with underlying CHF or with history of CHF	**Text in Local Swiss Labeling** **Warnings and Precautions** *Heart Failure* *Heart failure was reported more commonly in the two Phase 3 clinical trials in Zinplava-treated patients compared to placebo-treated patients. These adverse reactions occurred primarily in patients with underlying congestive heart failure (CHF). In patients with a history of CHF, 12.7% (15/118) of Zinplava-treated*	None

Table 3 Summary of Safety Concerns and Risk Minimisation Activities

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	patients and 4.8% (5/104) of placebo-treated patients had the serious adverse reaction of heart failure during the 12-week study period (see Adverse Reactions). Additionally, in patients with a history of CHF, there were more deaths in Zinplava-treated patients, 19.5% (23/118) than in placebo-treated patients, 12.5% (13/104) during the 12-week study period. The causes of death varied and included cardiac failure, infections, and respiratory failure. In patients with a history of CHF, Zinplava should be reserved for use when the benefit outweighs the risk. **Other Routine Risk Minimisation Measure(s)** Use of a CHF Specific Targeted Follow-Up Questionnaire	
Missing Information: Exposure in Patients 1 year to <18 years of age	**SmPC:** **Section 4.2 Posology and method of administration** *Section for Posology under Special Populations states that safety and efficacy of bezlotoxumab in patients below 18 years of age have not been established. No data are available.* **Package Leaflet:** **Section 2 What you need to know before you are given ZINPLAVA?** **Children and adolescents** *ZINPLAVA should not be used in children and adolescents below 18 years of age.*	None

2 Elements for a Public Summary

2.1 Overview of Disease Epidemiology

Clostridium difficile infection (CDI), also known as *C. difficile* associated diarrhea (CDAD), is a type of infection caused by bacteria that affects the colon. *C. difficile* produces two exotoxins, toxin A and toxin B, that target the gut causing changes and disruption of the normal intestinal barrier that is essential for the gut to function normally. Antibiotic use disrupts the normal flora of the gut, leading to excessive growth of *C. difficile* and CDI. CDI can cause complications, including death (mortality). The death rate due to CDI ranges between 5 to 10 per 100 patients, and increases with age. After treatment, CDI frequently recurs. One of the greatest challenges in managing CDI is to prevent its recurrence. For every 100 patients with CDI who are initially successfully treated, 15-35% will develop a recurrent infection. Among the clinical risk factors for recurrence of CDI are advanced age, having had a CDI in the past, and severity of the patient's underlying comorbidities.

2.2 Summary of Treatment Benefits

Bezlotoxumab is a fully human monoclonal antibody that binds and neutralizes *C. difficile* toxin B. In the two main studies, the medicine has been shown to be effective in the prevention of CDI recurrence relative to placebo in patients receiving concomitant standard of care (SoC) antibiotic therapy for the treatment of CDI. The two main studies included a total of 1563 adult patients with CDI who were receiving concomitant SoC antibiotics to treat CDI. The 1563 patients were then randomly assigned to receive either a single infusion of bezlotoxumab or an infusion without bezlotoxumab (placebo). All patients were observed for 12 weeks. At the end of the 12 week period 16.5% of patients treated with bezlotoxumab compared to 26.6% of patients treated with placebo experienced a recurrence of CDI. Bezlotoxumab significantly prevented CDI from recurring.

2.3 Unknowns Relating to Treatment Benefits

Bezlotoxumab is indicated for the prevention of recurrence of *Clostridium difficile* infection in adults at high risk for recurrence of CDI. Bezlotoxumab has been studied in male and female patients 18 to 100 years of age and in patients with renal and hepatic impairment. Bezlotoxumab has not been studied in patients less than 18 years of age or in pregnant or breastfeeding women.

2.4 Summary of Safety Concerns

Important Identified Risks

Table 4 Summary of Important Identified Risks

Risk	What is Known	Preventability
None		

Important Potential Risks

Table 5 Summary of Important Potential Risks

Risks	What is Known
Possibility of provoking immune defensive response of the body against the medicine (potential for immunogenicity)	Administration of any substance made from living organisms (biologics) has the ability to initiate formation of a protein (antibodies) against the medicine (anti-drug antibodies). In clinical studies, no subjects tested positive for antibodies against the medicine.
Impaired safety in patients with underlying CHF or with history of CHF	Heart failure was reported more commonly in the two Phase 3 clinical trials in Zinplava-treated patients compared to placebo-treated patients. These adverse reactions occurred primarily in patients with underlying congestive heart failure (CHF). In patients with a history of CHF, 12.7% (15/118) of Zinplava-treated patients and 4.8% (5/104) of placebo-treated patients had the serious adverse reaction of heart failure during the 12-week study period (see Adverse Reactions). Additionally, in patients with a history of CHF, there were more deaths in Zinplava-treated patients, 19.5% (23/118) than in placebo-treated patients, 12.5% (13/104) during the 12-week study period. The causes of death varied and included cardiac failure, infections, and respiratory failure.

Missing Information

Table 6 Summary of Missing Information

Missing Information	What is Known
Use in patients 1 to less than 18 years of age (exposure in patients 1 to <18 years of age)	Safety and effectiveness of bezlotoxumab in patients 1 to less than 18 years of age have not been studied and proven.

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 health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. The measures in these documents are known as routine risk minimisation measures.

The current Information for Professionals for Zinplava can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

2.6 Planned Post-authorisation Development Plan

2.6.1 List of Studies in Post-authorisation Development Plan

Table 7 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
(MK-6072-P001): Trial in Paediatric Patients Aged 1year to <18 years	Randomised, double-blind, single dose, placebo-controlled trial to evaluate, safety, tolerability, pharmacokinetics, and efficacy of a single infusion of bezlotoxumab (MK-6072, human monoclonal antibody to *Clostridium difficile* toxin B) as add-on to standard of care antibiotic treatment in children from 1 to less than 18 years of age with *Clostridium difficile* infection (CDI).	To determine a dosing recommendation for bezlotoxumab in the paediatric population and provide information on safety and efficacy in patients with CDI who are 1 year to < 18 years of age. In addition, ADA assessments will be conducted to assess the potential for immunogenicity.	Ongoing	Final Report: Nov 2022

2.6.2 Studies which are a Condition of the Marketing Authorisation

The above studies are conditions of the marketing authorisation.

2.7 Summary of Changes to the Risk Management Plan Over Time

This is version 2.2 and the second RMP for bezlotoxumab.

Table 8 Major Changes to the Risk Management Plan

RMP Version	Date	Safety Concerns	Comment
1.5	22-NOV-2016 (at the time of authorisation)	<u>Important identified risks</u> None <u>Important potential risks</u> Infusion-related Reactions Including Hypersensitivity and Anaphylactic Reactions Potential for Immunogenicity Potential Lack of Efficacy if Bezlotoxumab is Administered Off-label as Monotherapy Impaired safety in patients with underlying CHF or with history of CHF <u>Missing information</u> Exposure in patients <18 years of age Exposure in pregnancy/lactation Long Term Safety Repeated Administration of Bezlotoxumab	Initial Version

2.2	14-DEC-2020	Important identified risks None Important potential risks Potential for Immunogenicity Impaired safety in patients with underlying CHF or with history of CHF Missing information Exposure in patients 1 year to <18 years of age	Updated Version