Risk Management Plan (RMP) Summary

for

Zebinix® (eslicarbazepine acetate)

200 mg, 800 mg tablets

Final Version 1.0 (22 May 2020)

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 Zebinix® 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 Zebinix® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Bial, S.A. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zebinix®.

This RMP summary is based on Part VI of the EU RMP for Zebinix® (eslicarbazepine acetate) version 22.0, dated 02 March 2017

1 Elements for Summary Tables in the EPAR

1.1 Summary Table of Safety Concerns

Summary of safety concerns	
Important identified risks	
	Hyponatremia
	Cutaneous adverse reactions
Important potential risks	
	Thyroid function changes
	INR and aPTT increase
	Cardiovascular / cerebrovascular ischemia
	Potential for suicidality as anti-epileptic drug
	Bone disorders
Missing information	
	Exposure during pregnancy
	Pediatric population (< 2 years of age)
	Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children
	Elderly population

1.2 Table of On-Going and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

Not applicable.

1.3 Summary of Post Authorisation Efficacy Development Plan

There is no post-authorization efficacy development plan.

1.4 Summary Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hyponatremia	• Warning to monitor serum sodium levels before and during treatment with ESL; determine serum sodium levels if clinical signs of hyponatremia occur and during routine laboratory examination. If clinically relevant hyponatremia develops, ESL should be discontinued. • Listed as undesirable effect. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None.
Cutaneous adverse reactions	• Warning to stop therapy in case of signs or symptoms of hypersensitivity; to screen and genetically test individuals of Han Chinese, Thai origin and other Asian populations at risk for HLA-B*1502 allele before starting treatment; to consider benefits of treatment for patients of European descent or Japanese origin, if they are known to be positive for HLA-A*3101. • Listed as undesirable effect. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic (including vasculitis,	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	leukocytoclastic vasculitis and purpura). • Prescription only medicine.	
Thyroid function changes	• Listed as undesirable effect. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None.
INR and aPTT increase	• Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None.
Cardiovascular / cerebrovascular ischemia	• Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None.
Potential for suicidality as antiepileptic drug	• Warning to monitor patients for signs of suicidal ideation and behaviors and to consider appropriate treatment and/or to seek medical advice if signs of suicidal ideation or behaviour emerge. • Included in safety monitoring in clinical studies. • Implemented as monitoring topic. • Prescription only medicine.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bone disorders	• Included in safety monitoring in clinical studies. • Implemented as monitoring topic (including osteocalcin increased, decreased bone mineral density, osteopenia, osteoporosis, and fracture). • Prescription only medicine.	None.
Exposure during pregnancy	• Caution should be exercised when prescribing ESL to pregnant or lactating women. • Monotherapy should be preferred whenever possible as treatment to reduce risk of congenital malformation. • Specialist advice to be provided to women who are likely to become pregnant or who are of child-bearing potential. • No sudden treatment discontinuation should be undertaken as this may lead to breakthrough seizures. • Vitamin K1 should be administered in last few weeks of pregnancy and to newborn to avoid bleeding disorders in newborn. • Breastfeeding should be discontinued during treatment with ESL. • Alternative, effective and safe method of contraception in addition to oral contraception necessary; non-clinical studies have shown	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	developmental effects in embryos. • Supplementation of folic acids before and during pregnancy to reduce possible contributory risk of fetal abnormality by antiepileptic treatment. • Implemented as monitoring topic. • Included in a Pregnancy Registry (EURAP Registry).	
Pediatric population (< 2 years of age)	• ESL is not recommended for use in children aged 6 years and below, as the safety and efficacy of ESL has not yet been established (in section 4.2 of the SmPC). • Studies BIA-2093-305 and BIA-2093-208 have been completed. • PIP (P/0197/2013; EMEA-000696-PIP02-M04) is ongoing. • Implemented as monitoring topic. • Prescription only medicine.	None.
Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	• Ongoing monitoring of long term effects of ESL on brain development, learning, intelligence, growth, endocrine function, puberty and child bearing potential in children. • Implemented as monitoring topic.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Prescription only medicine.	
Elderly population	• Implemented as monitoring topic. • Prescription only medicine.	None.

2 Elements for a Public Summary

2.1 Overview of Disease Epidemiology

Epilepsy is a disease of the central nervous system characterized by different kinds of seizures. It is relatively common (4 to 8 of 1000 people have the disease) and affects adults and children worldwide. In most people, the disease first occurs in childhood or older age, especially after the age of 65; first occurrence in younger adults is much less common.

People with relatives who have the disease or have experienced brain injury have an increased risk of developing epilepsy. Seizures can be provoked by triggers, e.g. reading, excitement, lack of sleep, alcohol, or fever.

People with epilepsy have a higher risk of dying than the general population. Premature death is often linked to severe disease-specific events like status epilepticus or accidents.

People with epilepsy are treated with one or several anti-epileptic drugs. Seizure control is the most important treatment goal and is achieved with these drugs in most people.

2.2 Summary of Treatment Benefits

The efficacy of eslicarbazepine acetate (ESL) as adjunctive therapy has been demonstrated in 4 clinical studies in 1703 adult patients with partial epilepsy not controlled by other medicines. All of the patients also received other epilepsy medicines. The main objective of these studies was to verify the reduction in the number of seizures. The percentage of subjects with ≥50% reduction in seizure frequency (1581 analyzed) was 22.2% for placebo (an inactive medicine), 22.9% for ESL 400 mg, 33.8% for ESL 800 mg, and 43.1% for ESL 1,200 mg daily. ESL 800 mg and 1,200 mg were more effective than placebo in reducing seizure frequency.

The efficacy of ESL in children with partial seizures was also studied. In one study involving 123 children aged 6 to 16 years, over 12 weeks ESL reduced the number of seizures by half in 51% of patients (42 out of 83). This compared with 25% of patients (10 out of 40) on placebo. A second study in children aged 2 to 18 years did not find a difference between ESL and placebo, this was explained by the fact that lower doses were used.

The efficacy of ESL as monotherapy treatment was demonstrated in a study in 815 adult patients. The patients were newly diagnosed with partial seizures with or without secondary generalization. This study was done in comparison with carbamazepine controlled-release (CBZ-CR), which is a

common treatment in this indication. During the 26-week evaluation period, 71.1% patients were classified as seizure free in the ESL group and 75.6% in the CBZ-CR group. The treatment effect observed during the 26-week evaluation period was maintained over 1-year of treatment.

The efficacy of ESL as conversion to monotherapy was demonstrated in 2 studies in 365 adult patients with partial seizures. Seizure-free rates during the entire 10-week monotherapy period were 7.6 % (1,600 mg) and 8.3% (1,200 mg) in one study and 10.0 % (1,600 mg) and 7.4 % (1,200 mg) in other study respectively.

2.3 Unknowns Relating to Treatment Benefits

Zebinix® is not recommended as adjunctive therapy for epilepsy in children aged 6 years and below, and patients with severe renal or hepatic impairment due to insufficient data.

Caution should be exercised in the treatment of pregnant and lactating women as there is limited safety information on the use of ESL in these patients. Caution should also be exercised in the treatment of elderly patients as there is limited safety information on the use of ESL in these patients.

2.4 Summary of Safety Concerns

Important identified risks

Risk	What is known	Preventability
Low blood salt levels (Hyponatremia)	May affect 1 to 10 users in 100. Uncommonly low blood salt levels may cause complications such as confusion, worsening of seizures, or decreased consciousness.	Measuring sodium in blood; contacting doctor when symptoms such as confusion, worsening of seizures or decreased consciousness develop which can be signs of low blood salt levels.
Skin side effects (cutaneous adverse reactions)	Skin rash may affect 1 to 10 users in 100. Hypersensitivity (allergic reactions) may affect 1 to 10 users in 1000. Very rare but serious skin side effects that involve mucous membranes, large areas of the skin, blisters, bloodshot skin may occur with treatment of the	Warning the patient not to take Zebinix® in case of allergy to eslicarbazepine acetate, other carboxamide derivatives (e.g. carbamazepine or oxcarbazepine) is known. Instructing the patient to immediately contact a doctor or a hospital if rash, swallowing or breathing

Risk	What is known	Preventability
	chemically related antiepileptic drugs carbamazepine and oxcarbazepine and it cannot be excluded to also occur with Zebinix®. Patients with certain gene variants are more likely to develop serious skin side effects to carbamazepine than those without these gene variants.	problems, swelling of lips, face, throat or tongue occur. The risk of serious skin reactions in patients of Han Chinese or Thai origin associated with carbamazepine or chemically-related compounds may be predicted by testing a blood sample of these patients.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Thyroid function changes	From animal studies it is suspected that Zebinix® may change thyroid function. Decreased thyroid hormone levels were reported in clinical studies with eslicarbazepine acetate. Whether this is relevant for the use in patients is currently unknown.
Impaired coagulation (INR and aPTT increase)	In some clinical studies, in 1 to 10 of 100 patients impaired coagulation (INR increase) was observed. Whether this is relevant for the use in patients is currently unknown.
Events caused by reduced blood supply of the heart and the brain (Cardiovascular / cerebrovascular ischemia)	In clinical studies in elderly patients, events caused by reduced blood supply of the heart or the brain occurred more often in elderly than in young patients. This is expected because the risk for these events increases when patients become older. At present, available data do not indicate that there is an increased cardiovascular or cerebrovascular risk in Zebinix® users.
Thoughts of self-injury or killing (Potential for suicidality as anti-epileptic drug)	A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves.
Bone disorders	There have been reports of bone disorders including osteopenia, osteoporosis (thinning of the bone) and fractures for some anti-epileptics. At present, available data do not indicate that there is an increased risk in Zebinix® users.

Missing information

Risk	What is known
Potential harm to an unborn child if the mother uses Zebinix® during pregnancy (exposure during pregnancy)	Research has shown an increased risk of birth defects in children of women taking anti-epileptic drugs. If such an increased risk is also associated with the use of Zebinix® is unknown.
Use in children younger than 2 years of age (Pediatric population (< 2 years of age))	Eslicarbazepine acetate is approved in children aged above 6 years, with partial-onset seizures with or without secondary generalisation. The safety and efficacy of ESL in children aged 6 years and below has not yet been established, and is still under clinical development for the use in children below 2 years of age. ESL is not approved in this age group. Zebinix® is not to be given to children aged 6 years and below.
Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children	The clinical data gathered of long-term use of ESL in children allow to present evidence that no deleterious effects on either cognitive, physical or physiological development are known. Nevertheless, the long-term effects on brain development, learning, intelligence, growth, endocrine function, puberty and child bearing potential will be monitored on an ongoing way.
Use in elderly people (Elderly population)	Data from clinical trials in the indication neuropathic pain indicate that skin rash and hyponatremia may occur more frequently in patients aged 65 years or older than in younger patients. Also, PMS data shows that hyponatremia is the most frequent event in patients aged ≥65. A clinical study investigating risks and benefits in 72 elderly patients has been completed. The results demonstrated that once daily doses of ESL 400 mg, 800 mg and 1,200 mg as adjunctive therapy in elderly subjects did not raise major safety concerns and were efficacious.

2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have an Information for Professionals (also known as 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 minimising them. An abbreviated version of this in lay language is provided in the form of the Information for Patients (also known as package leaflet - PL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PL for Zebinix® can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

2.6 Planned Post Authorisation Development Plan

List of studies in post-authorization development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
BIA-2093-402 (EURAP) Category: 3	Pregnancy Exposure Registry	Missing information: Exposure during pregnancy	Ongoing	Expected by December 2024

Studies which are a condition of the marketing authorization

None of the above study is conditions of the marketing authorization.

2.7 Summary of Changes to the Risk Management Plan over Time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
4.0	At time of authorization 21 April 2009	Identified Risks • Hyponatremia • Cutaneous adverse reactions Potential Risks • Thyroid function changes • INR and aPTT increase • Cardiovascular/cerebrovascular ischemia • Potential for suicidality as anti-epileptic drug Missing information • Exposure during pregnancy • Pediatric population • Elderly population • Interactions: inducing properties of ESL on: - CYP 3A4; -Carbamazepine	
5.0	14 December 2009	Maintained	1. Nervous system and psychiatric disorder safety information included

Version	Date	Safety Concerns	Comment
			2. Information in interactions between hormonal contraceptives and ESL included (completed study BIA-2093-128) 3. Hyponatremia information included (cases were reported and discussed in PSUR) 4. Information (post-marketing) on potential for pediatric off-label use included 5. Completed studies: BIA-2093-128, BIA-2093-207 6. Planned studies: BIA-2093-311
6.0	07 June 2010	1. Inducing properties of ESL on CYP3A4 and carbamazepine removed as important missing information	1. Completed studies: BIA-2093-124, BIA-2093-127, BIA-2093-129, BIA-2093-206 2. Information from studies BIA-2093-124 and BIA-2093-129 resolved issue of the inducing properties of ESL on CYP3A4 and carbamazepine 3. Planned studies: BIA-2093-402 (pregnancy registry)
7.0	14 June 2011	Maintained	1. Information on pregnancy and post-marketing experience updated 2. Completed studies: BIA-2093-130, BIA-2093-206OL, BIA-2093-207OL 3. Information on Study BIA-2093-401 updated (Elderly population)
8.0	10 September 2012	Maintained	1. Additional pharmacovigilance activity requested by CHMP for patients experiencing severe cutaneous reactions

Version	Date	Safety Concerns	Comment
			(Information on HLA Genotyping (HLA-A*3101 and HLA-B*1502) included in pharmacovigilance activities)
9.0	17 December 2012	Maintained	1. Inclusion of detailed instructions for follow-up of safety reports through a specific questionnaire (Serious Adverse Cardiovascular/Cerebrovascular reaction or Serious adverse cutaneous reaction) 2. Information included on severe cutaneous reactions and genotyping 3. Instructions included for follow-up procedures through specific questionnaires 4. Completed studies: BIA-2093-208 DB, BIA-2093-209, BIA-2093-210, BIA-2093-305 DB, BIA-2093-304DB 5. Updated information on post-marketing experience, EURAP pregnancy registry; Study 401 (Elderly population)
10.0	11 November 2013	1. Bone metabolism disorders, including osteocalcin increased, decreased bone mineral density, osteopenia, osteoporosis, and fracture) added as an important potential risk 2. Terms “Vasculitis”, “leukocytoclastic vasculitis”, and “purpura” added to the important identified risk cutaneous adverse reactions	1. Bone metabolism disorder was included to address the matter that long-term use of carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine, and sodium valproate is associated with a risk of decreased bone mineral density that may lead to osteopenia, osteoporosis and fractures

Version	Date	Safety Concerns	Comment
			(EMA/CHMP/PhVWP/945939/2011) 2. Additional terms included as events of special interest 3. Completed studies: BIA-2093-212, 093-046 (Sunovion) 4. Completed studies under reporting: BIA-2093-208, BIA-2093-305, BIA-2093-401 5. Updated information on post-marketing experience and ongoing clinical studies 6. Change of format of the Risk Management Plan, according to the Guideline on GVP Module V – Risk Management Systems
11.0	27 January 2014	Maintained	1. Update of the categorization of studies BIA-2093-401 and BIA-2093-402 to category 3 in Part III and Part VI 2. Protocols of category 3 studies presented in Annex 6
12.0	25 March 2014	Elderly population removed as missing information. Studies BIA-2093-305 and BIA-2093-208 have been completed but PIP (P/0197/2013; EMEA-000696-PIP02-M04) is ongoing. Other safety concerns maintained.	1. Updated information on completed studies: TEAE analysis by age of pediatric studies BIA-2093-208 and -305; TEAE analysis by age of elderly studies BIA-2093-301 to -304 and -401. 2. Completed studies: BIA-2093-208, BIA-2093-305, BIA-2093-307, BIA-2093-308, BIA-2093-401
13.0	20 June 2014	Elderly population maintained as missing information.	Elderly population was maintained as missing information as requested by CHMP.
14.0	26 June 2015	Version submitted in parallel with procedure	Updated information following completion of the pediatric

Version	Date	Safety Concerns	Comment
		EMA/H/C/000988/X/0050/G which is under evaluation following different timelines (under evaluation). Age group 2-18 years was removed from missing information. Pediatric population maintained as missing information for children below 2 years of age. Other safety concerns maintained.	development program with ESL for the age group 2-18 years, according to PIP (PIP No: EMEA-000696-PIP02-10-M05) and proposed indication for ESL use in children aged 2 years and above, with partial-onset seizures with or without secondary generalization, with respective posology, including new proposed oral suspension. Updated information on post-marketing experience and ongoing clinical studies. Questionnaire of serious adverse cutaneous reaction updated with inclusion of date and inclusion of specific question on previous allergies to related AEDs.
15.0	31 March 2016	Updated from version 13.0. Safety concerns maintained	Updated information following completion of the development program with ESL for monotherapy in partial-onset seizures in adults. Updated information on post-marketing experience and clinical studies. Updated questionnaire serious adverse cutaneous reactions included.
16.0	12 May 2016	Updated from version 14.0 Age group 6-18 years removed from missing information. Pediatric population maintained as missing information for children below 6 years of age. Other safety concerns maintained	Updated information concerning response of the list of questions – Day 120 (question 3.5.2)
17.0	22 July 2016	Updated from version 16.0 Pediatric population maintained as missing information for children below 2 years of age.	Updated information concerning response of the list of questions – Day 180

Version	Date	Safety Concerns	Comment
		Long term effects in children development added as missing information Other safety concerns maintained	
18.0	30 September 2016	Updated from version 17.0 The missing information term "Long term effects in children development" was replaced by "Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children" The age range for which safety and efficacy *of Zebinix* has not yet been established in children was corrected from "6 years and below" to "below 7 years of age". Other safety concerns maintained	Updated information concerning response of the list of questions – Day 180
19.0	11 October 2016	Updated from version 15.0 The section VI.2.3 of this Summary was updated to include that caution should be exercised in the treatment of elderly patients and in pregnant and lactating women as there is limited safety information on the use of ESL in these patients.	Updated information concerning response of the list of questions – Day 90 (monotherapy application)
20.0	25 November 2016	Merging of versions 18 and 19 after the positive opinion issued on 13 October 2016 by the Committee for Medicinal Products for Human Use (CHMP) recommending changes to the terms of the marketing authorisation for the medicinal product Zebinix. Zebinix is now	Updated information concerning response of the 2nd list of questions – Day 90 (monotherapy application)

Version	Date	Safety Concerns	Comment
		indicated as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.	
21.0	23 February 2017	Updated from version 20.0. Safety concerns maintained	Update information after submission of responses to 2nd Day 90 Request for additional information (monotherapy application).
22.0	2 March 2017	Updated from version 21.0. Safety concerns maintained	Update information after submission of responses to 2nd Day 90 Request for additional information (monotherapy application).