EU Risk Management Plan for Baclofen 10mg Tablets

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name):	Baclofen
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Muscle relaxants, Centrally acting agents. ATC code: M03BX01
Name of Marketing Authorisation Holder or Applicant:	Zista Pharma Limited
Number of medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Baclofen 10mg Tablets
Marketing authorisation procedure	National
Brief description of the product	<u>Chemical class</u> Gamma-aminobutyric acid derivative
	<u>Summary of mode of action</u> Baclofen is an antispastic agent acting at the spinal level. A gamma-aminobutyric acid (GABA) derivative, Baclofen is chemically unrelated to other antispastic agents. Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the $GABA_B$-receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by Baclofen.
	<u>Important information about its composition</u> None
Hyperlink to the Product Information	See module 1.3.1
Indication(s) in the EEA	Current: Baclofen is indicated for the relief of spasticity of voluntary muscle resulting from such disorders as: multiple sclerosis, other spinal lesions,

	e.g. tumours of the spinal cord, syringomyelia, motor neurone disease, transverse myelitis, traumatic partial section of the cord. Baclofen is also indicated in adults and children for the relief of spasticity of voluntary muscle arising from e.g. cerebrovascular accidents, cerebral palsy, meningitis, traumatic head injury. <u>Paediatric population</u> Baclofen is indicated in patients 0 to <18 years for the symptomatic treatment of spasticity of cerebral origin, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease. Baclofen is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.
	Proposed: N/A
Dosage in the EEA	Current: **Adults** Treatment should be started with a dosage of 15 mg daily, preferably in divided doses. The following gradually increasing dosage regimen is suggested, but should be adjusted to suit individual patient requirements. -5 mg Baclofen (half a tablet) 3 times a day for 3 days, -10 mg Baclofen (1 tablet) 3 times a day for 3 days, -15 mg Baclofen (one and half tablets) 3 times a day for 3 days, -20 mg Baclofen (2 tablets) 3 times a day for the next 3 days. A maximum daily dose of 100 mg is advised unless the patient is in hospital under careful medical supervision. **Paediatric population** Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), in 2-4 divided doses (preferably in 4 divided doses). The dosage should be cautiously raised at about 1 week intervals. The usual daily dose for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age, a maximum daily dose of 60 mg/day may be given. Baclofen tablets are not suitable for use in children below 33 kg body weight.
	Proposed: N/A

Pharmaceutical form(s) and strengths	Current: 10mg Tablets
	Proposed: N/A
Will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Summary of safety concerns	
Important identified risks	• Drug withdrawal
	• Overdose (including CNS depression)
	• Hypersensitivity
	• Peptic ulceration
Important potential risks	• Use in patients with pre-existing conditions (includes renal and urinary disorders, psychiatric and nervous system disorders, respiratory impairment, hepatic impairment, and cerebrovascular accidents)
	• Concomitant use with levodopa/carbidopa, antihypertensives, drugs causing CNS depression, lithium and drugs affecting renal function
	• Elevation of aspartate aminotransferase, blood alkaline phosphatase and blood glucose levels
	• Use during pregnancy and breast-feeding
Missing Information	• Use in children younger than 1 year of age

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

All risks mentioned in the product information were considered for inclusion. Risks considered to have low seriousness and low frequency and that were well defined in the product information were not considered important for inclusion in the list of safety concerns.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Medication error including overdose
	• Concomitant use with nephrotoxic drugs
	• Drug-induced elevation of aspartate aminotransferase, alkaline phosphatase and glucose levels
	• Risk of abuse or misuse
Missing Information	• Use during pregnancy
	• Use in children under the age of one year
	• Risks of off-label use to treat drug addiction

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risk, important potential risks and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks
None

Important potential risks
Medication error including overdose

Potential mechanisms:
Risk of accidental medication error is increased in the target treatment population as the prevalence of neurological dysfunction (e.g. visual impairment, cognitive dysfunction and motor weakness) is increased. Baclofen tablets are also available in different strengths which may be prescribed simultaneously and many patients will be receiving other pharmacotherapy. The risk of intentional overdose is also increased as the prevalence of psychiatric co-morbidity is increased in the target population.

Evidence source(s) and strength of evidence:
There have been many case reports in published literature detailing baclofen overdoses in adults. There are two type of intoxications; acute and chronic. Acute intoxication involves encephalopathy respiratory depression, muscular hypotonia and generalised hyporeflexia as symptoms. Chronic intoxication involves hallucinations, impaired memory, catatonia or acute mania.

There have been relatively few published reports of overdoses in children. However, they generally present with similar symptoms.

Characterisation of the risk:
Medication errors may result in increased adverse reactions or existing conditions being aggravated. The symptoms of overdoses of baclofen may be predicted from its safety profile at therapeutic doses and include muscular hypotonia, hypothermia, drowsiness, respiratory depression, coma and convulsions. There has also been an increase in overdoses from illicit use in recent years, which may be related to the increased interest in off-label use of high oral doses of baclofen for alcohol use disorders. Therefore, a maximum daily dose of more than 100 mg is not advised unless the patient is in hospital under medical supervision.

Risk factors and risk groups:
Children
Patients with renal impairment
Patients using baclofen in off-label situations including for alcohol use disorders
Patients concomitantly using CNS drugs
Patients with associated neurological dysfunction or psychiatric disorders
Elderly people

Preventability:
The SmPC recommends that patients with psychiatric disorders including suicidality should be treated cautiously and closely monitored by healthcare professionals and caregivers of patients.

Impact on the risk-benefit balance of the product:
This safety concern is not expected to modify the risk-benefit balance of the product, as long as the pharmacovigilance plan and risk minimisation measures are properly implemented.

Public health impact:
The potential impact in public health when baclofen is used as recommended in the SmPC, is expected to be low, providing that precautions and risk factors are taken into account.

Concomitant use with nephrotoxic drugs

Potential mechanisms:
Baclofen is excreted renally by glomerular filtration. Drug interactions may reduce the renal elimination of baclofen and increase the risk of toxicity.

Evidence source(s) and strength of evidence:
Section 5.2 of the SmPC and literature.

Characterisation of the risk:
Patients with renal impairment and those taking drugs affecting the kidney are advised to use baclofen with caution. Patients should also be carefully monitored to prevent toxicity or help in early detection.

Risk factors and risk groups:
Patients with renal impairment
Patients taking nephrotoxic drugs

Preventability:
The SmPC recommends that baclofen should only be given to patients with end stage renal failure if the expected benefits outweigh the potential risk and patients should be closely monitored. Section 4.5 warns that concomitant use of medicines that may alter renal function could lead to toxic effects and recommends close monitoring of renal function and clinical state.

Impact on the risk-benefit balance of the product:
This safety concern is not expected to modify the risk-benefit balance of the product, as long as the pharmacovigilance plan and risk minimisation measures are properly implemented.

Public health impact:
The potential impact in public health when baclofen is used as recommended in the SmPC, is expected to be low, providing that precautions and risk factors are taken into account.

Drug induced elevation of aspartate aminotransferase, alkaline phosphatase and glucose levels

Potential mechanisms:
Baclofen can rarely cause drug-induced hepatitis and hyperglycaemia.

Evidence source(s) and strength of evidence:
Literature

Characterisation of the risk:
Clinical and non-clinical research has demonstrated that baclofen use is associated with elevations in alanine transaminase and aspartate transaminase, and blood sugar.

Risk factors and risk groups:
Patients with liver diseases
Patients with diabetes mellitus

Preventability:
The SmPC recommends that baclofen should be used with caution in patients with hepatic dysfunction. Liver function and serum glucose should be monitored during treatment in patients with diabetes mellitus and/or hepatic dysfunction.

Impact on the risk-benefit balance of the product:
This safety concern is not expected to modify the risk-benefit balance of the product, as long as the pharmacovigilance plan and risk minimisation measures are properly implemented.

Public health impact:
The potential impact in public health when baclofen is used as recommended in the SmPC, is expected to be low, providing that precautions and risk factors are taken into account.

Risk of abuse or misuse
Potential mechanisms:
Abuse/misuse is defined as the improper use of something. Baclofen acts as a CNS depressant by stimulating GABAB receptors. Therefore, there is a risk of individuals abusing or misusing baclofen.

Evidence source(s) and strength of evidence:
If used for the approved indication the risk of abuse or misuse is low, hence there is limited published literature in relation to this risk. However, due to its CNS depressant properties baclofen may be used

off-label to treat alcohol, cocaine, gammahydroxybutyrate, tobacco and opiate addiction. The individuals in these situations may replace the addiction they are treating with baclofen addiction.

Characterisation of the risk:
There is limited data suggested a risk of abuse or misuse of baclofen.

Risk factors and risk groups:
Patients with alcohol addiction or addictions to other drugs.

Preventability:
The SmPC recommends that patients with a history of substance abuse should be treated cautiously and closely monitored.

Impact on the risk-benefit balance of the product:
This safety concern is not expected to modify the risk-benefit balance of the product, as long as the pharmacovigilance plan and risk minimisation measures are properly implemented.

Public health impact:
The potential impact in public health when baclofen is used as recommended in the SmPC, is expected to be low, providing that precautions and risk factors are taken into account.

SVII.3.2. Presentation of the missing information

Safety in pregnancy	
Evidence source:	Literature and section 4.6 of the SmPC
Population in need of further characterisation:	Pregnant women and neonates exposed in utero.
Anticipated risk/consequence of the missing information	Drug withdrawal reactions have been reported in neonates following exposure in utero. The risk of teratogenicity has not been adequately characterised.

Safety in children under the age of one year	
Evidence source:	Literature. SmPC does not recommend baclofen use in children weighing less than 33kg.
Population in need of further characterisation:	Children under the age of one year or with a body weight less than 33kg.
Anticipated risk/consequence of the missing information	The benefit-risk profile has not been established in this age group.

Risks of off-label use to treat drug addiction	
Evidence source:	Literature
Population in need of further characterisation:	Patients receiving baclofen off-label for the treatment of alcohol and substance dependence.
Anticipated risk/consequence of the missing information	Higher baclofen doses than licensed may be used in patients with risk factors for seizures and hepatic dysfunction. The risk of baclofen toxicity may be increased. The benefit-risk profile has not been established for off-label use.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Medication error including overdose
	• Concomitant use with nephrotoxic drugs

	• Drug induced elevation of aspartate aminotransferase, alkaline phosphatase and glucose levels
	• Risk of abuse or misuse
Missing Information	• Safety in pregnancy
	• Safety in children under the age of 1 year
	• Risks of off-label use to treat drug addiction

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will be conducted to identify and characterise the risks of the product.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

None.

Part IV: Plans for post-authorisation efficacy studies

None.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The safety information in the proposed product information is aligned to the reference medicinal product.

Part VI: Summary of the risk management plan

Summary of risk management plan for Baclofen 10 mg Tablets

This is a summary of the risk management plan (RMP) for Baclofen 10 mg Tablets. The RMP details important risks of Baclofen 10 mg Tablets, how these risks can be minimised, and how more information will be obtained about Baclofen 10 mg Tablet's risks and uncertainties (missing information).

Baclofen 10 mg Tablets summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Baclofen Tablets 10mg should be used.

I. The medicine and what it is used for

Baclofen 10 mg Tablets are used to reduce and relieve the excessive tension in your muscles (spasms) occurring in various illnesses such as cerebral palsy, multiple sclerosis, cerebrovascular accidents, spinal cord diseases and other nervous system disorders (see the SmPC for the full indication). It contains baclofen as the active substance and it is for oral use.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Baclofen 10 mg Tablets, together with measures to minimise such risks and the proposed studies for learning more about Baclofen 10 mg Tablet's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Baclofen 10 mg Tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Baclofen 10 mg Tablets are risks that need special management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Baclofen 10 mg Tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of

the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Medication error including overdose
	• Concomitant use with nephrotoxic drugs
	• Drug induced elevation of aspartate aminotransferase, alkaline phosphatase and glucose levels
	• Risk of abuse or misuse
Missing Information	• Safety in pregnancy
	• Safety in children under the age of 1 year
	• Risks of off-label use to treat drug addiction

II.B Summary of important risks

Medication error including overdose	
Evidence for linking the risk to the medicine	Literature and SmPC section 4.9
Risk factors and risk groups	Children Patients with renal impairment Patients using baclofen in off-label situations including for alcohol use disorders Patients concomitantly using CNS drugs Patients with associated neurological dysfunction or psychiatric disorders Elderly people
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2, 4.4 and 4.9* *PL section 3* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription medicine only.*

Concomitant use with nephrotoxic drugs	
Evidence for linking the risk to the medicine	Literature and SmPC section 5.2
Risk factors and risk groups	Patients with renal impairment Patients taking nephrotoxic drugs
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 and 4.5* *PL section 2 and 3* Other routine risk minimisation measures beyond the Product Information:

	Legal status: *Prescription medicine only.*

Drug induced elevation of aspartate aminotransferase, alkaline phosphatase and glucose levels	
Evidence for linking the risk to the medicine	Literature
Risk factors and risk groups	Patients with liver diseases Patients with diabetes mellitus
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 and 4.4* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription medicine only.*

Risk of abuse or misuse	
Evidence for linking the risk to the medicine	Literature and SmPC section 4.4
Risk factors and risk groups	Patients with alcohol addiction or addictions to other drugs.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription medicine only.*

Safety in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription medicine only.*

Safety in children under the age of 1 year	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.2 and 4.4 *PL section 2 and 3.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription medicine only.*

Risks of off-label use to treat drug addiction	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1* *PL section 1* Other routine risk minimisation measures beyond the Product Information: Legal status: *Prescription medicine only.*

II.C Post-authorisation development plan

None.

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Baclofen 10 mg Tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Baclofen 10 mg Tablets.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

None.

Annex 4 - Specific adverse drug reaction follow-up forms

None.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

None.

Annex 6 - Details of proposed additional risk minimisation activities

None.

Annex 7 - Other supporting data (including referenced material)

None.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change