EU Risk Management Plan
For
Amglidia 0.6 mg/ml & 6 mg/ml (glibenclamide)

RMP version to be assessed as part of this application:

RMP Version number: 4.3

Data lock point for this RMP: 23 May 2025

Date of final sign-off: 26 February 2026

Rationale for submitting an updated RMP: The update is prepared following the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) issued in their Periodic Safety Update Report (PSUR) Assessment report of the PSUR covering the period (24 May 2022 to 23 May 2025) (Procedure number PSUSA/00010690/202505), requesting an update of the list of safety concerns.

Summary of significant changes in this RMP:

- Update of the RMP format in line with GVP Module V (Rev 2) (EMA/164014/2018 Rev.2.0.1).
- Update of Part II of the RMP with the latest information regarding post-authorisation exposure and the removal of the following safety concerns: 'Hypoglycaemia', 'Transitory increased transaminases', 'Neutropenia', 'Overdosing preservative sodium benzoate', 'Bullous eruptions, exfoliative dermatitis, erythema multiforme', 'Anaphylactic reaction including dyspnoea, hypotension and shock', 'Patients with renal or hepatic impairment' and 'Long-term use'.
- Part V and Part VI updated accordingly.
- Removal of Specific Adverse drug reaction follow up forms regarding Hypoglycaemia.

Other RMP versions under evaluation:

- Not applicable

Details of the currently approved RMP:

- Version number: 4.2
- Approved with procedure: EMEA/H/C/004379
- Date of approval (opinion date): 25 May 2018

QPPV name: Elise CHAUVEL

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French Regulatory Authority)
APHP	Assistance Publique - Hôpitaux de Paris
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
ATU	Temporary Authorisation for Use
CUA	Compassionate Use Access Authorisation
DEND	Developmental delay, Epilepsy, and Neonatal Diabetes syndrome
DLP	Data Lock Point
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
iDEND	intermediate-DEND syndrome
INN	International Non-proprietary Name
ISS	Investigator-Sponsored Study
IV	Intravenous
MAH	Marketing Authorisation Holder
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
UK	United Kingdom

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Glibenclamide
Pharmacotherapeutic group(s) (ATC Code)	A10BB01
Marketing Authorisation Holder	AMMTek
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	Amglidia 0.6 mg/ml oral suspension with 1 ml oral syringe. Amglidia 0.6 mg/ml oral suspension with 5 ml oral syringe. Amglidia 6 mg/ml oral suspension with 1 ml oral syringe. Amglidia 6 mg/ml oral suspension with 5 ml oral syringe.
Marketing authorisation procedure	Centralised in the European Union (EU) and national in United Kingdom (UK)
Brief description of the product	Chemical class Glibenclamide, a second-generation, short half-life sulphonylurea, is a hypoglycaemic agent that reduces blood-glucose by stimulating insulin release by the pancreas; this effect depends on the presence of active beta-cells or beta-cells made active by glibenclamide in the pancreatic islets in certain cases of neonatal diabetes.
	Summary of mode of action Sulphonylureas act on pancreatic beta-cells by inhibiting Adenosine triphosphate (ATP)-sensitive potassium channels. The mechanisms of action proposed for this effect include stimulation of insulin release by beta-cells of the pancreas.
	Important information about its composition This medicinal product contains 5 mg benzoate salt in each mL oral suspension. Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
Hyperlink to the Product Information	Module 1, section 1.3.1.
Indication(s) in the EEA	Current: Amglidia is indicated for the treatment of neonatal diabetes mellitus, for use in newborns, infants and children. Sulphonylureas like

	Amglidia have been shown to be effective in patients with mutations in the genes coding for the β-cell ATP-sensitive potassium channel and chromosome 6q24-related transient neonatal diabetes mellitus.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current: Glibenclamide suspension therapy should be initiated by a physician experienced in the treatment of patients with very early onset diabetes. To avoid exceeding sodium benzoate acceptable daily dose, Amglidia daily dose should not exceed 1 mL/kg/day. As a consequence, Amglidia 0.6 mg/mL should not be used for posology higher than 0.6 mg/kg/day. In any other cases, Amglidia 6 mg/mL should be preferred. Amglidia therapy should be initiated at 0.2 mg/kg per day in two divided doses before feeding (including bottle feeding) and increased by 0.2 mg/kg/day until insulin independence is achieved. Patients must be closely monitored by their treating physician during the titration phase
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): 0.6 mg/ml, oral suspension 6 mg/ml, oral suspension
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Amglidia is indicated for the treatment of neonatal diabetes mellitus, for use in newborns, infants and children.

Incidence and prevalence:

Neonatal diabetes with existing insulin secreting cells is a form of diabetes that is diagnosed usually in the first 6 months of life and unfrequently up to one year of age. This condition is distinct from the more common type 1 diabetes (which occurs later).

Neonatal diabetes with existing insulin secreting cells affects less than 0.01 in 10,000 people in the EU This is equivalent to a total of fewer than 500 people.

Demographics of the population in the authorised indication – and risk factors for the disease:

Neonatal diabetes mellitus is diabetes appearing within the first 6 months of life and a type of monogenic diabetes. neonatal diabetes mellitus is caused by many genes, most of which have an impact on pancreatic β cell formation or/and function, leading to extremely reduced or absent plasma insulin levels. In a small percentage of patients, neonatal diabetes mellitus (often in alternation with hypoglycaemia) is caused by mutations in genes affecting insulin action. In addition, neonatal diabetes mellitus is also linked to genes regulating the immune system, representing a distinct subtype [Barbetti, 2024].

The main existing treatment options:

The initial approach to hyperglycaemia includes assessing the quantity of glucose being administered and reducing the GIR when it does not affect patient nutrition and growth. In the neonate, ideal glucose infusion rates should be 6-12 mg/kg/minute to maintain appropriate minimums for growth without inefficient conversion of energy to fat. Patients with hyperglycaemia are initially managed on an intravenous insulin infusion. Guidelines for dosing and titrating insulin infusions in neonates are lacking in the literature. In studies assessing early insulin therapy in very low birth weight infants, an initial dose of 0.05 units/kg/hour was commonly used [Lemelman, 2018].

Sulfonylurea-responsive mutations are the most common cause of neonatal diabetes. Up to 90-95% of patients with NDM caused by KCNJ11 may be successfully transitioned completely off of insulin therapy with significant decrease in glycated haemoglobin levels and a decrease of hypoglycaemia events [Lemelman, 2018].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Signs and symptoms are mild-to-severe hyperglycaemia within the first post-natal months with clinical manifestations at diagnosis that may include intra-uterine growth restriction, hyperglycaemia, polyuria, severe dehydration, and failure to thrive, that can eventually be associated with developmental defects (such as macroglossia and umbilical hernia) or eventually with neurological and neuropsychological defects ranging from mild psychomotor retardation to severe developmental delay with treatment-resistant epilepsy and muscle weakness.

Neonatal diabetes with existing insulin secreting cells is life threatening and debilitating in the long term because of high blood sugar levels consequences and the risk of ketoacidosis.

Neonatal diabetes with existing insulin secreting cells cannot be prevented. It is a detectable condition that needs most often emergency treatment with Intravenous (IV) fluid and insulin, which is the only method so far to re-establish metabolic control. One has to remember that the condition puts newborns at short-term risks such a ketoacidosis, dehydration and death. The first goal of treatment is therefore to normalize blood glucose and reestablish normal hydration in these very young children. This is best done by IV fluids and insulin. Then subcutaneous or intravenous insulin therapy is delivered to these very young children to keep metabolic control. Insulin is difficult to handle because of the very small weight. The therapeutic margins are low between hypoglycaemia and hyperglycaemia, both harmful to the neurological development of the newborn. Moreover, it is to be noted that insulin is only a treatment of the hyperglycaemic symptoms but not a specific treatment targeting both the metabolic and neurological aspects often present in neonatal diabetes.

Important co-morbidities:

Literature describes developmental delay with or without epilepsy (DEND and iDEND syndromes) in 18% of probands with KATP channel mutations. They evidenced developmental coordination disorder (particularly visual-spatial dyspraxia) or attention deficits in all 27 probands (KATP subtype) unaffected by developmental delay or epilepsy who underwent in-depth neuropsychomotor and neuropsychological investigations (median age, 7 years [0·4-19]). Compared to the KATP subtype, the 6q24 subtype had specific features: developmental defects involving the heart, kidneys, or urinary tract (8/36, 22% vs. 2/71, 3%, p=0·002), intrauterine growth restriction (34/37, 92% vs. 34/70, 48%, p<0·001), and early diagnosis (median age, 5 days [1- 120] vs. 45·5 days [1-278], p<0·001). The authors concluded that NDM is often associated with neuropsychological dysfunction and developmental defects which are specific to the underlying genetic abnormality [Busiah, 2013].

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- key issues identified from acute or repeat-dose toxicity studies

    - *Single and repeat-dose toxicity*

    Glibenclamide was well tolerated after single dose administrations with very high doses, the oral LD50 values reported as greater than 1500 mg/kg in the mouse, rat and guineapig, and greater than 10000 mg/kg in the rabbit and dog.

    - *Repeated-dose toxicity*

    Repeat dose studies were of up to 18 months duration in rats and dogs and 12 months in rabbits. The 45-day and 9-week studies in rats used dose levels up to 2000 and 1000 mg/kg/day, respectively. There was no effect on blood glucose levels when measured at the end of the 45-day study, but levels were initially reduced in the 9-week study with a maximum effect during the first week of treatment and returning to control levels by the end of the study. No adverse effects were reported in either study with investigations covering body weight, food consumption, haematology, blood biochemistry, urinalysis, macroscopy, organ weights and histopathology. Dose levels in the 6- and 18-month studies in rats were up to 2000 mg/kg/day (6 months) and 300 mg/kg/day (18 months). The 6-month study showed only minor effects with partial enlargement of the islets of Langerhans and calcification of the renal tubular epithelia apparent at 200 and 2000 mg/kg/day and only a slight effect at the lower doses. Raised blood glucose levels were observed at all dose levels (30, 100 and 300 mg/kg/day) in the 18-month study together with a reduction in pancreatic β-cell granulation seen at all dose levels, although only very slight at the lowest dose.

    A decrease in β-cell granulation was also observed after 12 months treatment of rabbits with 100 and 300 mg/kg/day, and blood glucose levels were reduced after 3 months treatment but were slightly increased at the end of the full 12 months treatment. The 6-month rabbit study was conducted at lower doses (up to 42 mg/kg/day) with hypoglycaemia also reported together with increased BUN at the mid and high doses and decreased serum protein at the high dose, but since these effects were not reported in the longer 12-month study, which also used higher doses, their toxicological significance remains unclear.

    Administration of glibenclamide to dogs for 12 months at dose levels of 30, 100 and 300 mg/kg/day showed a decrease in blood glucose levels at all doses, and which was apparent at 6 months and maintained over the whole 12-month dosing period. This was also reported in the 6-, 12- and 18-month studies which were carried out with a maximum dose of 20 mg/kg/day. A decrease in β-cell granulation was also reported at the high dose in the 18-month study. Overall, few adverse effects of glibenclamide were reported in these dog studies, the only mention being gastrointestinal irritation in the 18-month study and small atrophic thymus at all three dose levels of 30, 100 and 300 mg/kg/day in the 12-month study.

    - *Reproductive/developmental toxicity*

    No formal juvenile toxicity studies with glibenclamide have been identified. However, examination of the details of the animals used in the repeat-dose toxicity studies together with appreciation of the exposure of foetuses and pups in the reproductive toxicity studies does address this point.

Results from these studies showed glibenclamide to have very few adverse effects even at the highest dose.

- *Genotoxicity*

Glibenclamide was not genotoxic in a limit set of assays for gene mutations and other genotoxic effects.

- *Carcinogenicity*

No formal carcinogenicity studies with glibenclamide have been reported however the 18-month repeat dose studies in rats do provide information and conclude that it showed no carcinogenic effects.

Based on the available non-clinical data, no findings of toxicological relevance to human use have been identified. The non-clinical studies do not indicate any safety concerns requiring inclusion in the safety specification. All non-clinical aspects of glibenclamide are adequately addressed by the existing information in the SmPC, and no additional non-clinical investigations or risk minimisation activities are warranted.

Part II: Module SIII - Clinical trial exposure

Clinical development of glibenclamide in neonatal diabetes included studies using standard tablets, crushed tablets and oral suspension formulations. Information on the pooled data from exposure from clinical trials published in the literature is presented in the table below.

A total of 71 patients were included in these studies which were submitted as part of the marketing authorisation application:

Table SIII.1: Clinical trial exposure

	Babenko, 2006	Pearson, 2006	Beltrand, 2015	Neogli, 2016
Number of patients (n)	2	44	18*	10*
Gender	50% male	55% male	72% male	70% male
Age at initiation (year)	Median 10.62 (4.75-16.5)	Median 6 (3 to 12)	Median 5.3 (0.1-18.5)	Median 0.65 (0.2-4.9)
Dose (mg/kg/day)	Median 0.40 (0.22-0.59)	Median 0.45 (0.05-1.50)	Median 0.2 (0-1.43)	Median 0.12 (0.06-0.57)
Duration of treatment	-	Max. 2 years	18 months	Median 2.3 years (0.02-11.30)

*Three patients included in the Neogli 2016 study were already part of Beltrand 2015 trial.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Porphyria

Reason for exclusion: Patients with porphyria should not receive the drug as it can exacerbate acute attacks and can cause severe photosensitivity reactions.

Is it considered to be included as missing information?: No

Rationale: SmPC section 4.3 states that the product is contraindicated in patients with porphyria.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Neonatal diabetes has an orphan disease designation in the EU; therefore, the population available for clinical studies is limited.

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare and very rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not applicable since the product is indicated in neonatal diabetes.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program Subjects with renal or hepatic impairment were not specifically studied in the clinical development programme. These conditions are uncommon in the paediatric population, and no safety concerns are inferred from these limitations.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Amglidia was initially available in France under a nominative Temporary Authorisation for Use (ATU) starting on 20 July 2015, and this status progressively transitioned to a Compassionate Use Access Authorisation (CUA) on 01 July 2021. This ATU corresponded to compassionate use granted by the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM), on a case-by-case basis, to ensure early access for patients with no therapeutic alternative. Subsequently, the product obtained a European Marketing Authorisation on 24 May 2018. The official commercial launch of both dosages (0.6 mg/ml and 6 mg/ml) in France started on 05 June 2024, replacing the ATU/CUA frameworks.

Amglidia is distributed through commercial channels in Germany (since 12 May 2020) and in the UK (since 01 October 2019). As mentioned above, this product is also distributed through commercial channels in France since 05 June 2024. Due to the impossibility of knowing the exact number of patients exposed to the product during commercial distribution, an estimate of patient exposure based on sales figures is provided.

It is considered that in average, one bottle of Amglidia is required per month for one patient's treatment (considered for a child weighting between 3 and 12 kg). Although prescribed doses for one month would be below the total amount of the product contained in one bottle of Amglidia (30 ml), the vials must be discarded 30 days after opening, regardless of the remaining content.

Therefore, patient exposure has been estimated as per the following formula:

Patients-months = total number of units distributed / 1 bottle per patient per month.

SV.1.2 Exposure

The cumulative numbers of Amglidia units distributed under the early access programs, are presented in the table below:

Table SVI: Cumulative distribution through [redacted]

Country / distribution	Estimated number of patients			
	AMGLIDIA 0.6 mg/ml	AMGLIDIA 0.6 mg/ml switched to 6 mg/ml	AMGLIDIA 6 mg/ml	Total
[redacted]	65	9	13	87

Sales figures (units sold) are provided to estimate patient exposure through commercial channels. These data are summarised in the following table:

Table SVII: Cumulative sales data since Launch date* to 23 May 2025[redacted]

Product	Product	Units sold	Patient-months
[redacted]	AMGLIDIA 0.6 mg/ml	[redacted]	**489**
[redacted]		[redacted]	**480**
[redacted]		[redacted]	**591**
AMGLIDIA® 0.6 mg/ml		**1,560**	**1,560**

[redacted]	AMGLIDIA 6 mg/ml	[redacted]	[redacted]
AMGLIDIA 6 mg/ml		**120**	**120**
Total		**1,680**	**1,680**

*Launch dates: Germany (12 May 2020), UK (01 October 2019), France (05 June 2024).

[redacted]

In total, 1,680 units of the product have been cumulatively sold (equivalent to approximately 1,680 patient-months). In addition, 87 patients were cumulatively treated with Amglidia through ATU/CUA distribution [redacted].

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and potential risks

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

This section is not applicable since this is an update of the RMP v4.1 which was drafted under the EMA/838713/2011 Rev 1* which is a superseded version.

The list of safety concerns included in previous RMP (v4.2) was as follows:

Table SVII.1: Summary of safety concerns in RMP v4.2

Summary of safety concerns	
Important identified risks	• Hypoglycaemia
Important potential risks	• Transitory increased transaminases • Neutropenia • Overdosing preservative sodium benzoate • Bullous eruptions, exfoliative dermatitis, erythema multiforme • Anaphylactic reaction including dyspnoea, hypotension and shock • Hypoglycaemia due to mix ups of the different presentations
Missing information	• Patients with renal or hepatic impairment • Long-term use

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

'Hypoglycaemia' previously classified as important identified risk has been removed from the list of safety concerns.

'Transitory increased transaminases', 'Neutropenia', 'Overdosing preservative sodium benzoate', 'Bullous eruptions, exfoliative dermatitis, erythema multiforme' and 'Anaphylactic reaction including dyspnoea, hypotension and shock', previously classified as important potential risks have been removed from the list of safety concerns.

'Patients with renal or hepatic impairment' and 'Long-term use' previously classified as missing information have been removed from the list of safety concerns.

The removal of the above risks is based on the recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC) issued in their Periodic Safety Update Report (PSUR) Assessment report of the PSUR covering the period 24 May 20022 to 23 May 2025 (Procedure number PSUSA/00010690/202505).

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

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

Important Potential Risk: Hypoglycaemia due to mix ups of the different presentations *(Medication errors (broad scope) in situations of mix-up dosing. In cases also reporting events under the MedDRA SMQ Hypoglycaemia and Hypoglycaemic and neurogenic shock and conditions (narrow scope))*

Potential mechanisms:

Glibenclamide is a hypoglycaemic agent. Hypoglycaemia can occur if the doses are not correctly adjusted.

Evidence source(s) and strength of evidence:

As there are two dosages with two presentations each, there is a potential risk of medication errors, including dispensing errors by pharmacists, which could lead to severe hypoglycaemia.

Characterisation of the risk:

- Clinical experience

  One case of mix-ups occurred during the NEOGLI study. The pharmacy delivered a wrong dosage form (6 mg/mL instead of 0.6 mg/mL). A human error was identified as the cause. The patient experienced an overdose that led to hypoglycaemia (assessed as non-serious), that has been resolved by eating an ice-cream.

- Post-marketing experience

  According to the Company's Safety Database, no post-marketing cases related to mix-ups between presentations leading to hypoglycaemia have been reported to date.

Severe hypoglycaemia, if not corrected, could lead to seizure or loss of consciousness.

Risk factors and risk groups:

Pharmacists dispensing the product and patients switching between presentations, or patients of low weight needing low doses, may be a higher risk.

Preventability:

The product information clearly advises on the proper dosing for Amglidia. Care is advised when prescribing and administering the product to avoid dosing errors between mg and ml. It should be ensured that the proper dose and strength are communicated and dispensed.

Since Amglidia is administered with an oral syringe graduated in mL, the calculated daily dose should be expressed in mL by the physician explicitly stating the strength to be used.

The syringe will be chosen (1 mL or 5 mL) based on the volume in mL to be administered for each dose, as prescribed by the physician. The 5 mL syringe has to be used for volumes greater than 1 mL.

The nearest volume to the calculated one should be used.

In addition, as per the Risk management Plan (RMP), there are additional Risk Minimisation Measures (RMMs) in place to minimise this risk. All Healthcare Professionals (HCPs) who are expected to prescribe Amglidia, have access to an educational guide (prescriber's guide) aimed to increase awareness about the four presentations available for the product (two strengths of the product, each containing either a 1mL or a 5mL syringe) and at minimising the risk of hypoglycaemia in case of mix-ups of the different presentations.

Impact on the risk-benefit balance of the product:

Hypoglycaemia can sometimes be severe and prolonged. Hospitalization may then prove necessary, and glucose may have to be administered for several days. Potential manifestations of severe hypoglycaemia are pallor, sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, and problems with consciousness.

Therefore, the impact on daily living, quality of life and psychological well-being of the individual, may be significant.

Public health impact:

Glibenclamide is indicated only in a specific and limited population and as a result the overall impact on public health is considered to be minimal, providing that precautions and risk factors are taken into account.

SVII.3.2. Presentation of the missing information

Not applicable.

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	Hypoglycaemia due to mix ups of the different presentations
Missing information	None

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

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place for Amglidia.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place for Amglidia.

III.3 Summary Table of additional Pharmacovigilance activities

There are no ongoing or planned categories 1-3 safety studies for Amglidia.

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies were imposed for Amglidia.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hypoglycaemia due to mix ups of the different presentations	Routine risk communication: *SmPC section 4.2* *PL section 3* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Not applicable.* Other routine risk minimisation measures beyond the Product Information: Legal status: *Medicinal product subject to medical prescription.*

V.2. Additional Risk Minimisation Measures

Educational material – Prescribers guide to ensure Amglidia is used correctly:

Objectives:

The guide will increase prescribers and patient's parents/carers awareness on the different medicine presentations and help avoid medication errors.

Rationale for the additional risk minimisation activity:

Amglidia is available as an oral suspension in two strengths: 0.6 mg/ml and 6 mg/ml, and each strength is available in two presentations: either with a 1-ml oral syringe or with a 5-ml oral syringe. The strength and the size of the oral syringe to be used depends on the dose prescribed. It is important that only the syringe provided with the pack is used to measure Amglidia.

Dosing errors may occur due to confusion between milligram (mg) and millilitre (ml), or use of incorrect strength or size of syringe and how the dose is measured, which may result in too high or too low blood sugar levels.

To avoid medication errors, prescribers will be given a guide specifying which strength and presentation to use and what details to include on each prescription.

Target audience and planned distribution path:

All healthcare professionals who are expected to prescribe Amglidia will be provided with a guide to help ensure that the medicine is prescribed and used correctly.

HCPs should explain to the parent or carer that the dose of Amglidia is prescribed in ml according to the patient's body weight. HCPs should also explain that the dose is to be given with the oral syringe graduated in ml, provided in the pack.

Pharmacists should ensure that the correct strength of Amglidia and the correct size of oral syringe are dispensed.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness of this measure will be assessed through routine pharmacovigilance and presented in the PSURs.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypoglycaemia due to mix ups of the different presentations	Routine risk minimisation measures: *SmPC section 4.2* *PL section 3* Legal status: *Medicinal product subject to medical prescription.* Additional risk minimisation measures Prescribers Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Amglidia (glibenclamide)

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

Amglidia's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Amglidia should be used.

This summary of the RMP for Amglidia should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Amglidia's RMP.

I. The medicine and what it is used for

Amglidia is indicated for the treatment of neonatal diabetes mellitus, for use in newborns, infants and children (see SmPC for the full indication). It contains glibenclamide as the active substance and it is given by oral route.

Further information about the evaluation of Amglidia's benefits can be found in Amglidia's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/amglidia.

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

Important risks of Amglidia, together with measures to minimise such risks and the proposed studies for learning more about Amglidia'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.

In the case of Amglidia, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Amglidia are risks that need special risk 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 Amglidia. 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	Hypoglycaemia due to mix ups of the different presentations
Missing information	None

II.B Summary of important risks

Important potential risk	
Evidence for linking the risk to the medicine	As there are two dosages with two presentations each, there is a potential risk of medication errors including dispensing errors from pharmacists leading to severe hypoglycaemia. Severe hypoglycaemia, if not corrected, could lead to seizure or loss of consciousness.
Risk factors and risk groups	Pharmacists dispensing the product and patients switching between presentations or patients of low weight needing low doses.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 PL section 3 Additional risk minimisation measures Prescribers guide
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

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 Amglidia.

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

There are no studies required for Amglidia.

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Approved key messages of the additional risk minimisation measures

Prior to the use of Amglidia in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness about the four presentations available (two strengths of the product, each containing either a 1mL or a 5mL syringe) and at minimising the risk of hypoglycaemia in case of mix-ups of the different presentations.

The MAH shall ensure that in each Member State where Amglidia is marketed, all healthcare professionals who are expected to prescribe Amglidia have access to/are provided with the following educational package to be disseminated through professional bodies:

- Physician educational material

Physician educational material:

- A Prescriber's Guide, including the Summary of Product Characteristics (SmPC) attached.

The Prescriber's Guide shall contain the following key messages:

- Amglidia is a suspension to be administered with a provided oral syringe graduated in mL. Healthcare professionals or patients should never use another syringe than the one provided in the box to avoid dosing errors which could result in serious harm.
- Amglidia is available in four different boxes corresponding to four different presentations (four different strengths):
    - One box for the 0.6 mg/mL strength with one 1mL syringe: yellow colour for outer carton and reverse type yellow colour for label
    - One box for the 0.6 mg/mL strength with one 5 mL syringe: yellow colour for outer carton and reverse type yellow colour for label
    - One box for the 6 mg/mL strength with one syringe of 1 mL: purple colour for outer carton and reverse type purple colour for label
    - One box for the 6 mg/mL strength with one syringe of 5 mL: purple colour for outer carton and reverse type purple colour for label
- The choice of the Amglidia strength should be defined according to the prescribed posology and the patient's body weight.
- The Amglidia 0.6 mg/mL strength should not be used for posology higher than 0.6 mg/kg/day to limit the exposure to the sodium benzoate excipient. Please read the posology and method of administration in the SmPC attached to this prescriber guide.
- Choice of the syringe to be used:
    - After the total daily dose and the strength to be used have been defined, the frequency of the daily administration should be pointed out and the corresponding volume per administration should be calculated.
    - Depending on the volume calculated per administration:

- If the volume per administration is 1mL or below, the 1mL syringe should be prescribed;
- If the volume per administration is more than 1mL, the 5mL syringe should be prescribed.

- The prescription should state the calculated daily dose in mL, the strength of Amglidia to be used, the number of administrations over which the daily dose is divided, as well as the volume in mL to be administered for each dose and the size of the syringe to be used.
- Patients and/or their caretakers should be explained that:
  - They are prescribed a dose of Amglidia in mL according to their body weight. This dose is to be administrated with a provided oral syringe graduated in mL.
  - There are 2 presentations for a same strength: one with a syringe of 1mL and one with a syringe of 5 mL.
  - Patients or their caretakers should be reminded to use the correct syringe as stated in their prescription.
- If the patient is prescribed a different presentation, the prescriber should highlight to the patient the packaging differences between the different presentations (focus on colour differentiation, warning statements on carton, thickness and length of the provided syringe).