ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMGLIDIA 0.6 mg/mL oral suspension AMGLIDIA 6 mg/mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMGLIDIA 0.6 mg/mL oral suspension

Each mL contains 0.6 mg glibenclamide.

AMGLIDIA 6 mg/mL oral suspension

Each mL contains 6 mg glibenclamide.

Excipient(s) with known effect

Each mL contains 2.8 mg of sodium and 5 mg of benzoate (E211). For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral suspension.
White suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Glibenclamide suspension therapy should be initiated by a physician experienced in the treatment of patients with very early onset diabetes.

Prescription instructions

Care should be taken when prescribing and administering AMGLIDIA to avoid dosing errors due to confusion between milligram (mg) and millilitre (mL). It should be ensured that the proper dose and strength are communicated and dispensed.

Posology

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.

To limit exposure to sodium benzoate and with respect to the mode of delivery (1 mL and 5 mL oral

syringes), it is not recommended to use the AMGLIDIA 0.6 mg/mL strength for posologies higher than the ones described below:

Table 1 : Maximum recommended posology

Body weight (kg)	**Maximum recommended posology (expressed as mg/kg/day) where the AMGLIDIA 0.6 mg/mL strength can be used**
Up to 10	0.6
11	0.5
12	0.5
13	0.4
14	0.4
15	0.4
16	0.3
17	0.3
18	0.3
19	0.3
20	0.3

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.

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.

Patients should be closely monitored by their treating physician during the titration phase.

Inpatient treatment introduction

AMGLIDIA should be introduced at a dose of 0.2 mg/kg/day, in two administrations. Basal and bolus insulin should be administered on Day 1. On Day 2, if administered sub-cutaneously, basal insulin can be removed. If on insulin pump, basal rate of insulin pump should be reduced by 50% and should be further reduced in accordance with capillary blood-glucose measurements. Throughout the transfer period, bolus insulin or insulin pump boluses should be administered with meals as required to maintain reasonable glycemic control. From Day 2 until the end of the titration phase, if capillary blood glucose is ≥7 mmol/L, AMGLIDIA should be increased by 0.2 mg/kg/day. If capillary blood glucose is < 7 mmol/L, AMGLIDIA should not be increased and pre-meal insulin boluses should be reduced by 50%.

Pre-breakfast glucose may be very slow to fall. Pre-lunch or pre-evening meal glucose values fall more rapidly and are generally a better marker of response to AMGLIDIA.

The same protocol should be repeated every day until insulin independence is achieved. As soon as insulin is discontinued, the dose of AMGLIDIA is adjusted according to capillary blood glucose.

For patients still under insulin at day 6, the dose of AMGLIDIA should be maintained for at least

4 weeks. This may be done as an outpatient.

Patients can be discharged when no longer requiring insulin treatment, when stable on a combination of AMGLIDIA and insulin or when stable on insulin alone.

Outpatient treatment introduction

AMGLIDIA should be introduced at a dose of 0.2 mg/kg/day in two administrations and the dose should be progressively increased each week by 0.2 mg/kg/day.

As the dose is increased, it is usually possible to reduce and then stop the insulin dose.

From week 2 onward, if capillary blood glucose is ≥7 mmol/L AMGLIDIA should be increased by 0.2 mg/kg/day and insulin should be reduced. If capillary blood glucose is < 7 mmol/L insulin should be reduced.

If blood-glucose value increases after insulin reduction, AMGLIDIA should be increased by 0.2 mg/kg/day. Insulin reduction should be done using the pre-meal glucose.

The same protocol should be repeated every week until insulin independence is achieved. As soon as insulin is discontinued, the dose of AMGLIDIA is adjusted according to capillary blood glucose.

If at the end of a 5 to 6-week period, there is no evidence of a response with insulin doses similar to those at starting, administration of doses up to 2 mg/kg/day for a week may be tried (in rare cases, it has taken 4 months to wean off insulin completely).

If there is a clear reduction in insulin requirement at this dose of 2 mg/kg/day (reduction in insulin to at least 60% of pre-AMGLIDIA dose), then it is worth continuing a higher dose of AMGLIDIA over a prolonged period of time in selected cases.

Dose adjustments and long-term management

As shown in the literature and in the clinical studies performed with glibenclamide, the average daily dose is expected to be around 0.2 to 0.5 mg/kg/day in most of the patients suffering from neonatal diabetes. Higher doses have occasionally been observed and doses up to 2.8 mg/kg/day have been successfully given without adverse reactions, according to literature. In case of a partial response on lower doses, as shown by reduced insulin requirements, a further dose increase up to 2.8 mg/kg/day may be tried in selected cases.

In some children glycemic control can be better achieved when glibenclamide is administered 3 times or 4 times daily.

If no improvement is seen (unchanged insulin dose, similar glycaemic control and no improvement in neurology), AMGLIDIA should be discontinued.

During titration period patients' capillary blood-glucose concentration should continue to be monitored four times a day and at bedtime, as insulin requirements may continue to fall, or AMGLIDIA may need to be titrated. Once steady state is reached, capillary blood glucose does no longer need to be daily monitored except in clinical situations at risk of metabolic unbalance (see below). In all cases, HbA1c must be monitored every three months.
Sometimes, blood-glucose concentration will fall even though the patient is on a fixed dose of AMGLIDIA. Therefore, to avoid hypoglycaemia, consideration should be given to reducing the dose of AMGLIDIA or stopping treatment.

Reduction of AMGLIDIA dose should be anticipated by the treating physician and certainly if the glucose values are going below 4 mmol/L (72 mg/dL).

It may be necessary to adjust the dose of AMGLIDIA in patients suffering from intercurrent infections, trauma, shock or anaesthesia:

- For major surgery, insulin therapy should replace AMGLIDIA;
- Hepatic or renal dysfunction may require a reduction in dose;
- In exceptional situations of stress (e.g. trauma, surgery, febrile infections), blood-glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control.

Patients occasionally may have very high glucose values, i.e. > 20 mmol/L (> 360 mg/dL). In some cases these high glucose values seem to settle with the normal dose of AMGLIDIA. However, close monitoring of blood-glucose is required in all cases (please also refer to recommendations given under the heading "dose omission" further below) and adequate measures to restore euglycaemia (e. g. application of a third daily AMGLIDIA dose or insulin) must be taken.

Bioequivalence with tablets

AMGLIDIA is not bioequivalent with (crushed) tablets containing the same amount of glibenclamide. Available data are described in section 5.2.

Missed dose

If a dose is missed, there is a risk of hyperglycaemia. Blood-glucose level must be checked immediately and AMGLIDIA must be taken as soon as possible**.** If the blood-glucose level exceeds 16.5 mmol/L, the presence of ketonuria or ketonaemia must also be checked. If ketone bodies are present, an insulin injection must be given rapidly to restore the metabolic situation. The attending specialist should then be contacted.

Special populations

Renal impairment

Dose adjustment is required in patients with mild to moderate renal impairment. In those patients, treatment should be started at the lowest dose levels and should be strictly followed, to avoid hypoglycaemic reactions (see section 4.4). For severe renal impairment see section 4.3.

Hepatic impairment

Dose adjustment is required in patients with mild to moderate hepatic impairment. In those patients, treatment should be started at the lowest dose levels and should be strictly followed, to avoid hypoglycaemic reactions (see section 4.4). For severe hepatic impairment see section 4.3.

Elderly

Safety and efficacy of AMGLIDIA in elderly patients have not been established since the medicinal product is indicated in the paediatric population.

At risk patients

In malnourished patients or those displaying a marked change in their general condition, or whose calorie intake is irregular, and in patients with impaired renal or hepatic function, treatment should be started at the lowest dose levels and should be strictly followed, to avoid hypoglycaemic reactions (see section 4.4).

Method of administration

This medicinal product is administered orally as a “ready for-use” oral suspension using a graduated oral syringe. It is administered directly into the child's mouth. The bottle does not need to be shaken before administration.

Since no interaction study between glibenclamide and milk has been performed, and despite absence of food effect on glibenclamide absorption, recommendation is given to administer the suspension 15 minutes before child’s milk feeding.

Only the oral syringe included in the outer carton should be used.

Depending on the volume to be administered orally, there are two types of oral syringes, graduated up to 1 mL or up to 5 mL. Each syringe is included in a specific pack size. The appropriate syringe (1 mL or 5 mL), included in a specific AMGLIDIA pack size, will be prescribed by the physician based on the volume to be administered for each dose.
The two syringes, respectively included in two different pack sizes for each strength, are clearly distinguishable: 1 mL oral syringe is thin and small while 5 mL syringe is thick and long.

The dose to be administered is obtained by drawing the plunger back as far as the scale marking for the dose determined for each child. The dose in mL per administration and the number of administrations per day have to carefully follow the medical prescription.

Administration through a feeding tube should be avoided.

For instructions of the medicinal product before administration, see section 6.6.

4.3 Contraindications

This medicinal product is contraindicated in the following cases:
- hypersensitivity to the active substance, other sulphonylureas or sulphonamides or to any of the excipients listed in section 6.1;in patients with ketoacidosis, continuous intravenous insulin injection and intravenous infusion of physiologic sodium chloride solution remains the benchmark treatment.
- in patients with porphyria;
- in patients taking bosentan (see section 4.5)
- in patients with severe renal impairment
- in patients with severe hepatic impairment

4.4 Special warnings and precautions for use

Special care should be taken when calculating the dose. Before each administration, it should be verified that the correct strength and syringe are used (see section 4.2).

Glibenclamide should not be used in patients with insulin-dependent type 1 diabetes mellitus with evidence of auto-immune destruction of beta cells.

Patients with G6PD enzyme deficiency

In patients carrying a G6PD enzyme deficiency, cases of acute haemolytic anaemia have been reported with glibenclamide. It should therefore not be prescribed for these patients, and the use of an alternative treatment is strongly recommended, if available. If there is no alternative, the decision for each patient must consider the danger of haemolysis and the potential benefit expected from the treatment. If it is necessary to prescribe this medicinal product, screening should be conducted for the occurrence of any haemolysis.

Ketoacidosis

Neonatal diabetes is a life-threatening and chronically debilitating condition due to hyperglycemia, which includes symptoms such like thirst, frequent urination, and dehydration. In severe cases this is associated with ketoacidosis which can led to death. Glibenclamide should not be used to treate this life-threatening condition. Continuous intravenous insulin injection and intravenous infusion of physiologic sodium chloride solution remains the benchmark treatment.

Hypoglycaemia

Hypoglycaemia can occur under treatment with hypoglycaemic sulphonamides. This can sometimes be severe and prolonged. Hospitalisation may then prove necessary and glucose may have to be administered for several days.

Diarrhoea, nausea and vomiting

In some patients, there may be an initial diarrhoea when the dose of glibenclamide suspension is increased but it settles if the dose is maintained.
In case of nausea glycaemia seems to be maintained and insulin does not need to be re-introduced until the patient is able to take the glibenclamide suspension.
If there is major vomiting, a fast-acting insulin should be used to treat the patient until vomiting stops.
If there is minor vomiting, an antivomiting medicinal product should be given and treatment with glibenclamide can be continued.

Biological analyses

Blood-glucose should be monitored periodically throughout treatment with glibenclamide. If the blood-glucose level exceeds 16.5 mmol/L, the presence of ketonuria or ketonaemia must also be checked. If ketone bodies are present, an insulin injection must be given rapidly to restore the metabolic situation.

The glycosylated haemoglobin level should be measured every three months to assess the child's metabolic equilibrium.

Renal impairment

Patients with renal impairment should be monitored periodically during treatment due to the increased risk of hypoglycaemia. Dose adjustment is required in patients with mild to moderate renal impairment (refer to section 4.2).

Hepatic impairment

Patients with hepatic impairment should be monitored periodically during treatment due to the increased risk of hypoglycaemia. Dose adjustment is required in patients with mild to moderate hepatic impairment (refer to section 4.2).

Sodium

This medicinal product contains 2.8 mg of sodium per mL oral suspension, equivalent to 0.1% of the WHO recommended daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

Benzoic acid and benzoates (sodium benzoate)

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).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed for the two oral suspensions of glibenclamide (0.6 mg/mL and 6 mg/mL).

Hypoglycaemia may occur when taking other medicinal products.

Highly protein-bound medicinal products, which may also potentiate the hypoglycaemic action of glibenclamide due to glibenclamide displacement from plasma proteins, include oral anticoagulants, phenytoin, salicylates and other non-steroidal anti-inflammatory agents.
Weakening of the blood-glucose-lowering effect and, thus, raised blood-glucose levels may occur when taking other medicinal products.
Under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent. The symptoms of hypoglycaemia may also be milder or absent where hypoglycaemia develops gradually or where there is autonomic neuropathy.

In very rare cases, an intolerance to alcohol may occur. Both acute and chronic alcohol intake, or excessive alcohol ingestion by people who drink occasionally, may attenuate the hypoglycaemic effect of glibenclamide or dangerously potentiate it by delaying its metabolic inactivation. Disulfiram-like reactions have occurred very rarely following the concomitant use of alcohol and glibenclamide.

Glibenclamide may increase ciclosporin plasma concentration and potentially lead to its increased toxicity. Monitoring and dose adjustment of ciclosporin are therefore recommended when both medicinal products are co-administered.

Colesevelam binds to glibenclamide and reduces glibenclamide absorption from the gastrointestinal tract. No interaction was observed when glibenclamide was taken at least 4 hours before colesevelam. Therefore, glibenclamide should be administered at least 4 hours prior to colesevelam.

Summary of interactions

A summary of the interactions detailed above and further interactions are summarized in the table below.

Table 2 : Summary of interactions

Active substance	**Effect of interaction**	**Potential risk**
ACE inhibitors	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Acetazolamide	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Adrenaline (epinephrine) and other sympathomimetic agents	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Alcohol	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
	Attenuation of the hypoglycaemic effect of glibenclamide or dangerously potentiating it	Incorrect control of plasma glucose

	by delaying its metabolic inactivation	
Anabolic steroids and male sex hormones	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Barbiturates	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Beta-receptor blockers	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
	Signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent	Incorrect control of plasma glucose
Biguanides	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Bosentan	Increase liver enzymes	Incorrect control of plasma glucose
Calcium channel blockers	Weakening of the blood-glucose-lowering effect	Increased blood-glucose levels
Chloramphenicol	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Cimetidine	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Clarithromycin	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Clonidine	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
	Potentiation or weakening of the blood-glucose lowering effect	Incorrect control of plasma glucose
	Signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent	Incorrect control of plasma glucose
	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Colesevelam	Reduction of glibenclamide absorption from the gastrointestinal tract	Incorrect control of plasma glucose
Corticosteroids	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Coumarin derivatives	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
	Potentiate or weaken the effect of coumarin derivatives	Incorrect dose of coumarin derivatives administered
Cyclophosphamides	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Diazoxide	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Disopyramide	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Diuretics	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels

Fenfluramine	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Fenyramidol	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Fibrates	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Fluoxetine	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Glucagon	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Guanethidine	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
	Signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent	Incorrect control of plasma glucose
H2-receptor antagonists	Potentiation or weakening of the blood-glucose lowering effect	Incorrect control of plasma glucose
Heparin	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Ifosfamide	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Insulin	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Isoniazid	Weakening of the blood-glucoselowering effect	Increased blood-glucose levels
Large doses of laxatives	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Long-acting sulphonamides	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
MAO inhibitors	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Miconazole	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Nicotinic acid (in high doses)	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Oestrogens	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Other oral antidiabetics	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Oxypentifylline	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Oxyphenbutazone	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Phenothiazine derivatives	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Phenytoin	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Phosphamides	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Probenecid	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Progestogens	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Quinolone antibiotics	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Reserpine	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
	Potentiation or weakening of	Incorrect control of plasma

	the blood-glucose lowering effect	glucose
	Signs of adrenergic counter-regulation to hypoglycaemia may be reduced or absent	Incorrect control of plasma glucose
Rifampicin	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Thyroid hormones	Weakening of the blood-glucose lowering effect	Increased blood-glucose levels
Salicylates	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Sulfamethoxazole with trimethoprim (Co-trimoxazole)	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Tetracycline compounds	Potentiation of the blood-glucose lowering effect	Hypoglycaemia
Tritoqualine	Potentiation of the blood-glucose lowering effect	Hypoglycaemia

4.6 Fertility, pregnancy and lactation

General aspects

AMGLIDIA is indicated for the treatment of neonatal diabetes in newborns, infants and children.

Women of childbearing potential

Women of childbearing potential planning a pregnancy should be switched from oral glibenclamide to insulin. Glibenclamide should not be given during pregnancy.

Pregnancy

Based on a limited amount of published data, the use of glibenclamide during the first trimester does not seem to cause an increase in congenital malformations. With respect to the second and third trimester published data did not find fetotoxic effects.
Animal studies do not indicate a teratogenic potential.

Glibenclamide crosses the placenta mostly in small amounts; however, transfer is highly variable among patients.

In pregnant women insulin is recommended for blood sugar control. Breast-feeding

Published data from 11 glibenclamide-treated mothers indicate that glibenclamide is not excreted in human milk and hypoglycaemia in the breast-fed newborns was not reported. Breast-feeding seems to be compatible, but as a precautious measure monitoring of the fully breast-fed infant’s blood sugar level is advisable.

Fertility

Clinical data are not available.

4.7 Effects on ability to drive and use machines

Glibenclamide has moderate influence on the ability to drive and use machines since it may increase the risk of hypoglycaemia. This may not be relevant for the target population. However, reduced alertness may also be of concern when participating in road traffic (e.g. cycling) or in play (e.g. skateboarding).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are hypoglycaemia, transitory diarrhoea and abdominal pain. The most serious adverse reaction is hypoglycaemia (see section 4.4).
Overall, the safety profile of glibenclamide is in line with the safety profile of others sulfonylureas.

Tabulated list of adverse reactions

Adverse reactions reported with glibenclamide (oral suspension or crushed tablets) in children, in the frame of treatment of neonatal diabetes are listed below by system organ class and frequency grouping. Frequencies are defined as:
Very common (≥ 1/10);
Common (≥ 1/100 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (< 1/10,000);
not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions

MedDRA system organ class		
Adverse reactions	Very common	Common
Blood and lymphatic system disorders	Neutropenia	
Eye disorders		Vision blurred
Metabolism and nutrition disorders	Hypoglycaemia	
Gastrointestinal disorders	Transitory diarrhoea, Abdominal pain,Vomiting Dyspepsia	Tooth discolouration
Investigations	Transitory increased transaminases	
Skin disorders	Skin rash	

Description of selected adverse reactions

The following adverse reactions have been observed in a clinical study (Neogli study) and during the extension phase. This was a phase II, single-centre, prospective, open-label, non-randomised study. After enrolment, patients continued taking their usual doses of glibenclamide tablets for 1 month. Ten patients were switched to glibenclamide oral suspension and treatment with oral suspension continued for 3 months.

Hypoglycaemia

Two cases of severe hypoglycaemia were observed, which were considered related to the medicinal product. Symptomatic measures were taken and the situation resolved in the two cases.

Transitory diarrhoea, vomiting and abdominal pain and dyspepsia

Two children had abdominal pain (one with transient diarrhoea and vomiting during the same episode) that were considered related to the medicinal product. Symptomatic measures were taken and the medicinal product continued and the situation resolved in the two cases.

One child had dyspepsia, which was considered related to the medicinal product. Symptomatic measures were taken and the situation resolved.

Neutropenia and transitory increased transaminases

One child had punctually low leucocytes level, but close to the normal range (neutrophils 1.3×10^3/microliter for a lower limit of normal of 1.5×10^3/microliter).
The same child had a transient and minimal ASAT 73 IU/L, and ALAT 42 IU/L increased (normal range below 60 and 40 respectively). These resolved subsequently.

Skin disorders

One child experienced isolated skin rash.

The following other adverse reaction has been collected from post marketing sources.

Eye disorders

One child experienced filmy vision: Visual disturbances can be due to fluid moving into and out of the eye due to high blood sugar levels.

The following adverse effects have been observed in adult patients treated with other products containing glibenclamide. These adverse effects have been not observed with AMGLIDIA but may occur:

Eye disorders

Transient visual disturbances (blurred vision or accommodation disorder) have been reported, especially early in treatment without glycaemic variation.

Skin and subcutaneous tissue disorders

In isolated cases photosensitivity may occur.
Skin rash, pruritus, urticaria, allergic skin reaction, bullous eruptions, exfoliative dermatitis and erythema multiforme have occasionally been reported in adults.

Immune system disorders

Anaphylactic reaction including dyspnoea, hypotension and shock have been reported.

Blood disorders

Blood affections have been observed, generally reversible when treatment stops.
Hypereosinophilia, leucopenia, mild or severe thrombocytopenia have been reported, which can lead to purpura. Rare cases of agranulocytosis, haemolytic anaemia, bone marrow aplasia and pancytopenia have also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose of sulphonamides can result in hypoglycaemia.
The symptoms of moderate hypoglycaemia, without loss of consciousness or neurological signs, must be completely corrected by taking sugar, adjusting the dose and/or changing dietary behaviour. Close monitoring of blood-glucose by the patient's family must be continued until the family and the physician, if he/she had to be contacted, are certain that the patient is out of danger.
Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and are medical emergencies requiring immediate treatment as soon as the cause is diagnosed or suspected before immediately admitting the patient to hospital.

If a hypoglycaemic coma is diagnosed or suspected, the patient should quickly receive an intravenous injection of concentrated glucose solution (0.5 g/kg body weight as a 30% glucose solution). This must be followed by continuous infusion of more dilute glucose solution (10%) at the rate needed to maintain blood-glucose above 100 mg/dL (100 mg/dL = 5.5 mmol/L). Patients must be closely monitored for at least 48 hours and, depending on the patient's condition at this time, the physician will decide if additional monitoring is necessary.

Plasma clearance of glibenclamide may be prolonged in patients suffering from liver disease. Due to strong binding of glibenclamide to proteins, dialysis is of no benefit to the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, sulphonylureas, ATC code: A10BB01

Mechanism of action

Sulphonylureas act on pancreatic beta-cells by inhibiting ATP-sensitive potassium channels. The mechanisms of action proposed for this effect include stimulation of insulin release by beta-cells of the pancreas.
The minimum active concentration for the effect is considered to be 30-50 ng/mL glibenclamide.

Pharmacodynamic effects

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.

Stimulation of insulin secretion by glibenclamide in response to a meal is of major significance. Administering glibenclamide to a diabetic enhances the post-prandial insulinotropic response. Post-prandial responses involving secretion of insulin and peptide-C continue to be enhanced after at least 6 months of treatment and even over many years in the case of neonatal diabetes by potassium channel disorders.

Glibenclamide has 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.

Clinical efficacy and safety

Treatment using sulphonylureas in neonatal diabetes linked to potassium channel disorders is supported by published studies showing measurable improvements in glycaemic control and suggesting neuro-psychomotor and neuro-psychological deficiencies, which are greater in younger patients.

From data published in the literature, treatment with sulfonylurea is reported to be successful in approximately 90% of the patients with neonatal diabetes associated with K-ATP channel mutations. The average dose reported in the literature (clinical studies and case reports) is of approximately 0.5mg/kg/day. When limited to clinical studies or prospective data collections only, the average dose decreases to 0.2 to 0.3 mg/kg/day. Higher doses have occasionally been reported in the literature with doses as high as 2.8 mg/kg/day without undesirable effects and with full transfer off insulin.

In a phase II, single-centre, prospective, open-label, non-randomised study, acceptability, efficiency and tolerance of the switch from crushed tablets to glibenclamide suspension were measured. Ten patients (7 boys/3 girls) with KCNJ11 mutation, with median age 2.7 years (0.3 to 16.2) and median duration of glibenclamide therapy 2.3 years (6 days to 11.3 years) were treated.
Daily doses ranged from 0.1 to 0.8 mg/kg for glibenclamide tablets (median dose, 0.3 mg/kg) and from 0.1 to 0.6 mg/kg for oral suspension (median 0.1 to 0.2 mg/kg/day over the study period) given in 2 to 4 administration per day).

After switching from glibenclamide tablets to glibenclamide suspension, there was no significant change in glycaemic control as evidenced from the similar serum HbA1c (6.5 vs 6.1% at Visits M0 and M4, respectively; p=0.076) and fructosamine (283.4 vs 271.2 µmol/L at Visits M0 and M4, respectively; p=0.55) mean concentrations.

None of patients experienced deterioration in glycaemic control, defined as an increase of HbA1c by > 0.5% and exceeding 5.6% in patients with baseline HbA1c ≤ 5.6% or an increase of HbA1c by > 0.5% in patients with baseline HbA1c > 5.6%.

A large international long-term term study of treatment for neonatal diabetes due to *KCNJ11* mutations is ongoing and results were reported in 81 patients of the 90 patients originally included with a median [interquartile range] follow-up duration of 10.2 years [9.3-10.8 years]. Transfer to sulfonylureas occurred in childhood with a median [IQR] at transfer of 4.8 years [1.7 – 11.4 years]. Seventy-five patients (93%) remained on sulphonylurea alone at most recent follow-up and 6/81(7%) were on sulphonylurea and daily insulin. In patients on sulphonylurea alone, blood glucose control has been improved after transfer to sulfonylureas with median [IQR] HbA1c of 5.9% [5.4-6.5%] at 1 year vs 8.0 % [7.2-9.2 %] before transfer (p < 0.0001), and remained very well controlled after 10 years with a median [IQR] HbA1c of 6.4% [5.9-7.2 %].

The median [IQR] dose of sulfonylurea fell over the follow-up with a median [IQR] dose of 0.30 mg/kg/day [0.14-0.53] mg/kg/day at one year and of 0.23 mg/kg/day [0.12-0.41 mg/kg/day] at 10 years, p=0.03). There were no reported episodes of severe hypoglycaemia. Adverse reactions (diarrhoea/nausea/reduced appetite/abdominal pain) were reported in 10/81(12%); these were transient, and no patients discontinued sulphonylurea as a result. Microvascular complications were reported in 7/81(9%) patients; there were no macrovascular complications. Patients with complications were older at age of transfer to sulfonylurea than those without complications (median age at transfer: 20.5 v 4.1 years, p=0.0005). Oral glucose tolerance tests and intravenous glucose tolerance tests revealed good insulin response to glucose and maintained incretin effect after ten years.

Evidence exists that administration of glibenclamide might improve some neurological deficits in patients with neonatal-onset diabetes due to *KCNJ11* or *ABCC8* mutations like epilepsy, motor function and hypotonia, by a mechanism independent from insulin secretion.
Earlier treatment initiation might be associated with greater benefits.

5.2 Pharmacokinetic properties

Absorption

After oral administration, glibenclamide is absorbed rapidly and induces its effect within 2.5 hours with a duration of up to 15 hours, although the elimination half-life is 5 to 10 hours. The food effect on the speed or the level of absorption of glibenclamide oral suspension has not been investigated.

Bioavailability studies have demonstrated that nonmicronised tablets provide serum glibenclamide concentrations that are not bioequivalent to those from micronised tablets.

Head to head comparative pharmacokinetic data following the application of glibenclamide suspension and micronised tablets are not available. The conversion rate between micronised tablets and the suspension has not been established.

A comparative study of relative bioavailability between two suspensions of glibenclamide oral suspensions (0.6 mg/mL and 6 mg/mL) and crushed glibenclamide tablets (Daonil 5 mg) showed that when glibenclamide oral suspensions were administered, peak plasma concentrations of glibenclamide are reached 0.5 hours earlier than that observed with the crushed Daonil tablet (median value after administration is 2.5 hours compared to 3 hours). The values for maximum plasma concentrations (C_{max}) were similar for the two suspensions (201.71 ± 71.43 ng/mL for the 6 mg/mL suspension and 206.93 ± 67.33 ng/mL for the 0.6 mg/mL suspension). These values were approx. 40% greater than those obtained for the crushed tablet (148.34 ± 46.74 ng/mL).

The exposures were respectively similar for the two glibenclamide oral suspensions, and greater than those observed after administration of crushed Daonil tablets. The relative bioavailability was 121.6% for the 0.6 mg/mL suspension and 114.1% for the 6 mg/mL suspension compared to the crushed Daonil tablets.

Population pharmacokinetic approach was used to compare steady state concentrations following 0.9 mg twice daily in children with body weights between 10 – 30 kg and 1.25 mg twice daily in adults. The plasma glibenclamide levels in the simulated paediatric population were approximately 30%-60% lower than the adult levels. With smaller bodyweight the concentration increased but exceeded the adult plasma levels in minimal extents only for poor metabolizers.

Distribution

Glibenclamide is strongly bound to plasma albumin (99%), which may account for certain drug interactions, but is not easily detached by acidic medicinal products.

Biotransformation and elimination

Glibenclamide is completely metabolised by the liver into 3 inactive metabolites excreted via bile (60%) and urine (40%); elimination is complete in 45 to 72 hours. Clinical studies appear to suggest that CYP2C9 contributes significantly to glibenclamide metabolism *in vivo*.
Liver failure reduces the metabolism of glibenclamide and therefore significantly slows down its elimination.Biliary excretion of the metabolites increases in the event of kidney failure, proportionally to the severity of the change in renal function. Kidney failure does not affect its elimination as long as creatinine clearance remains above 30 ml/min.

The elimination half-lives were similar for the two suspensions (almost 8 hours) and a little shorter than those observed with the crushed Daonil tablets.

5.3 Preclinical safety data

In repeated dose toxicity studies with oral administration of high doses of glibenclamide, effects on pancreatic beta-cells were observed (enlargement of the islets of Langerhans with irregularly configured islets and reduction in pancreatic β-cell granulation in rats at doses of ≥ 30 mg/kg/day, beta-cell exhaustion as indicated by depletion of insulin-containing granules in rabbits at doses of 100 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

hydroxyethylcellulose lactic acid
purified water
sodium benzoate (E211) sodium citrate
xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening

30 days.
Keep the bottle tightly closed.

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Brown glass bottle (type III) with a child-resistant closure (polypropylene screw cap with polyethylene capsule inside) in a carton containing a 1 mL or 5 ml graduated oral syringe of LDPE and polypropylene depending on the pack size prescribed and an adaptor (LDPE) to be plugged on the bottle after opening for the syringe.

The 1 mL oral syringe is thin and small and graduated in steps of 0.05 mL. The 5 mL syringe is thick and long and graduated in steps of 0.1 mL.

Pack sizes

One bottle of 30 ml suspension and one oral syringe of 1 mL packed in an individual bag and one syringe adaptor.

One bottle of 30 ml suspension and one oral syringe of 5 mL packed in an individual bag and one syringe adaptor.

6.6 Special precautions for disposal and other handling

At the first use, the bottle should be opened by unscrewing the child-resistant closure while pressing downwards. The adaptor should be inserted firmly into the bottle while holding the bottle the right way up. The screw cap should then be replaced on the bottle with the adaptor and not removed during the 30-day use. The screw cap should be retightened in order to push the adaptor well into the bottle.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AMMTeK
8 rue Campagne Première

75014 Paris
France
Tel: + 33 (0)6 74 29 38 14

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1279/001
EU/1/18/1279/002
EU/1/18/1279/003
EU/1/18/1279/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 May 2018
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENT OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Euromed Pharma France
1 Rue de la Chaudanne
69290 Grézieu-la-Varenne
France

Centre Spécialités Pharmaceutiques 76-78 Avenue du midi
63800 Cournon d'Auvergne France

Unither Pharmaceutical
Zone d'Activites Tech Espace Avenue Toussaint Catros 33185 Le Haillan
FRANCE

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

At the request of the European Medicines Agency;
Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

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

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 the following educational guide:

A Prescriber's Guide, including the SmPC of AMGLIDIA is 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 pack sizes (four different strengths):
  - ➢ One box for the 0.6 mg/mL strength with one 1 mL 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's 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 1 mL or below, the 1 mL syringe should be prescribed;
  - ✓ If the volume per administration is more than 1 mL, the 5 mL 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 pack sizes 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 pack size, the prescriber should highlight to the patient the packaging differences between the different pack sizes (focus on colour differentiation, warning statements on carton, thickness and length of the provided syringe).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AMGLIDIA 0.6 mg/mL oral suspension glibenclamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 0.6 mg glibenclamide.

3. LIST OF EXCIPIENTS

Contains sodium and benzoate, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension. 1 x 30 mL bottle.
1 oral syringe (1 mL).
1 oral syringe (5 mL).
1 syringe adaptor.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

You should only use the syringe which has been prescribed by your doctor.
Make sure you have the box containing the syringe size prescribed by your doctor.
If a new pack size of AMGLIDIA is prescribed by your doctor, return back your previous pack size and syringe to your pharmacist to avoid mixing up of the syringes.

8. EXPIRY DATE

EXP
After opening, keep the bottle tightly closed after each use and stored for a maximum of 30 days.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from the light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AMMTeK
8 rue Campagne Première
75014 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1279/001
EU/1/18/1279/002

13. BATCH NUMBER

Lot

14. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

15. INDICATIONS D'UTILISATION

16. INFORMATION IN BRAILLE

AMGLIDIA 0.6 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

AMGLIDIA 0.6 mg/mL oral suspension glibenclamide

Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Keep out of the sight and reach of children.

3. EXPIRY DATE

EXP
Keep the bottle in the outer carton in order to protect from the light.
After opening, keep the bottle tightly closed after each use and stored for a maximum of 30 days.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mL

6. OTHER

Each mL contains 0.6 mg glibenclamide.

Contains sodium and benzoate, see leaflet for further information.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AMGLIDIA 6 mg/mL oral suspension glibenclamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 6 mg glibenclamide.

3. LIST OF EXCIPIENTS

Contains sodium and benzoate, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension. 1 x 30 mL bottle.
1 oral syringe (1 mL).
1 oral syringe (5 mL).
1 syringe adaptor.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

You should only use the syringe which has been prescribed by your doctor.
Make sure you have the box containing the syringe size prescribed by your doctor.
If a new pack size of AMGLIDIA is prescribed by your doctor, return back your previous pack size and syringe to your pharmacist to avoid mixing up of the syringes.

8. EXPIRY DATE

EXP
After opening, keep the bottle tightly closed after each use and stored for a maximum of 30 days.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from the light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AMMTeK
8 rue Campagne Première
75014 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1279/003
EU/1/18/1279/004

13. BATCH NUMBER

Lot

14. CONDITIONS DE PRESCRIPTION ET DE DÉLIVRANCE

15. INDICATIONS D'UTILISATION

16. INFORMATION IN BRAILLE

AMGLIDIA 6 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

AMGLIDIA 6 mg/mL oral suspension glibenclamide

Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Keep out of the sight and reach of children.

3. EXPIRY DATE

EXP
Keep the bottle in the outer carton in order to protect from the light.
After opening, keep the bottle tightly closed after each use and stored for a maximum of 30 days.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mL

6. OTHER

Each mL contains 6 mg glibenclamide.

Contains sodium and benzoate, see leaflet for further information.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

AMGLIDIA 0.6 mg/mL oral suspension

glibenclamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of your child.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AMGLIDIA is and what it is used for

Amglidia contains the active substance called glibenclamide which belongs to a group of medicines called sulphonylureas used for lowering blood sugar (blood-glucose).

Amglidia is used in newborns, infants and children to treat diabetes that occurs at birth (known as neonatal diabetes mellitus). Neonatal diabetes is a disease where the child's body does not release enough insulin to control the level of blood sugar; Amglidia is used only in patients who still have some ability to make insulin.
Sulphonylureas like glibenclamide have been shown to be effective in certain genetic mutations responsible for the genesis of neonatal diabetes.

This medicine is an oral suspension, to be taken by mouth, which is a more convenient treatment for newborns and children compared to regular injections of insulin.

You must talk to a doctor if your child does not feel better or if he/she feels worse after a few days.

2. What you need to know before you give AMGLIDIA

Do not give AMGLIDIA

- if your child is allergic to glibenclamide or any of the other ingredients of this medicine (listed in section 6).
- if your child has ketoacidosis (high blood levels of acid substances called ketones).
- if your child suffers from porphyria (inability to break down body chemicals called porphyrins).
- if your child is treated with bosentan, e.g. a medicine used to treat problems of blood circulation.
- if your child suffers from severe renal dysfunction.
- if your child suffers from severe liver dysfunction

Warnings and precautions

Talk to your doctor before your child is given Amglidia.

Your child's blood sugar levels may become too low (hypoglycaemia) after taking Amglidia. Tell the doctor if your child is pale, sweating, has irregular heart rhythm or seems disoriented, confused or unresponsive. See also section 4. Too low blood sugar (hypoglycaemia).

Ask your doctor to determine at which frequency capillary blood sugar should be checked.

G6PD is an enzyme evolved in sugar metabolism. If your child carries a G6PD enzyme deficiency, he/she may experiment an abnormal breakdown of red blood cells (acute haemolytic anaemia) after taking Amglidia.
Tell the doctor if you know that your child is affected by G6PD deficiency and contact him/her if you notice that your child is pale as compared to usually.

Tell your doctor if your child suffers from renal or liver disorders.

Your child may experience diarrhoea when the dose of glibenclamide suspension is increased but it will be transitory if the dose is maintained.
Your child may experience nausea. If your child is able to take the glibenclamide suspension, do not stop the treatment.
Talk to your doctor if your child experienced vomiting, the doctor may decide to treat your child with insulin until vomiting stops in case of major vomiting.
The doctor may also decide to treat your child with an anti-vomiting medicine in case of minor vomiting. In this case, Amglidia will be continue.

Children and adolescents

Amglidia is to be used for newborns, infants and children.

Other medicines and AMGLIDIA

Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines as some medicines while taking Amglidia, may give more side effects or affect the way Amglidia is working.

It is especially important to inform your child's doctor or pharmacist of the following:

These medicines may decrease the amount of sugar in your blood when taken with Amglidia:
- ACE inhibitors (such as captopril and enalapril), used to treat high blood pressure (hypertension)
- Anabolic steroids and male sex hormones (such as testosterone enanthate), used to treat low testosterone levels (testosterone deficiency)
- Biguanides (such as metformin), used to treat diabetes mellitus
- Chloramphenicol (taken by mouth), an antibiotic used to treat infections
- Clarithromycin, an antibiotic used to treat certain infections
- Cyclophosphamides, used to treat different types of cancer
- Disopyramide, used to treat an irregularity in the heart beat
- Fibrates (such as bezafibrate, fenofibrate, gemfibrozil), used to lower the level of fats
- Fluoxetine, used to treat depression and anxiety disorders
- Heparin, used to decrease the clotting ability of the blood
- Ifosfamide, used to treat different types of cancers
- Insulin, used to lower the amount of sugar in the blood (blood sugar level)
- MAO inhibitors (such as iproniazide), used to treat depression
- Miconazole, used to treat fungal infection
- Other oral antidiabetics (such as metformin), used to lower the amount of sugar in the blood (blood-glucose level)
- Oxypentifylline, used to improve blood flow in the extremities (peripheral blood flow)
- Probenecid, used to treat gout, gouty arthritis

- Quinolone antibiotics (such as nalidixic acid and ciprofloxacine), used to treat infections
- Sulfamethoxazole with trimethoprim (Co-trimoxazole), used to treat infections
- Salicylates (such as aminosalicylic acid, para-aminosalicylic acid), used for tuberculosis
- Tetracycline antibiotics (such as doxycycline and minocycline), used to treat infections

These medicines may increase the amount of sugar in your blood when taken with Amglidia:
- Acetazolamide, used to treat damage to the nerve in the eye (glaucoma)
- Adrenaline (epinephrine and other sympathomimetic agents), used to treat serious allergic reaction, the abrupt loss of heart beat (cardiovascular arrest), asthma
- Barbiturates (such as phenobarbital), used to treat epilepsy
- Calcium channel blockers (such as nifedipine), used to treat high blood pressure
- Cimetidine, used to relieve the symptoms of stomach and duodenal ulcers, to treat the disease where stomach acid rises up into the oesophagus (oesophageal reflux disease), and to treat the Zollinger-Ellison syndrome
- Corticosteroids (such as prednisone, prednisolone), used in various indications such as inflammation and asthma
- Diazoxide, used for low blood sugar
- Diuretics (such as furosemide, hydrochlorothiazide), used to treat high blood pressure in the arteries (arterial hypertension)
- Glucagon, used to treat high amounts of sugar in the blood (high blood-glucose level)
- Isoniazid, used to treat tuberculosis
- Large doses of laxatives (such as macrogol)
- Nicotinic acid (in high doses), used to decrease high levels of cholesterol and triglycerides which are fat-like substances in the blood
- Oestrogens (such as 17-beta oestradiol), used for hormonal treatment
- Phenothiazine derivatives (such as chlorpromazine), used to treat schizophrenia and other psychoses
- Phenytoin, used to treat epilepsy
- Progestogens (such as desogestrel, dydrogesterone), used for hormonal treatment
- Rifampicin, used to treat infections including tuberculosis
- Thyroid hormones (such as L-thyroxin), used for hormonal treatment

These medicines may decrease the amount of sugar in your blood or may hide low sugar levels when taken with Amglidia
- Beta-receptor blockers (such as propranolol), used to treat high blood pressure (hypertension), to control irregular or fast heart beats, or to help prevent additional heart attack

These medicines may affect the amount of sugar in your blood (either increase, decrease or both) and/or the control of sugar in plasma when taken with Amglidia
- Bosentan, used to treat high blood pressure (hypertension) in the blood vessels between the heart and the lungs.
- Clonidine, used to treat high blood pressure in the arteries (arterial hypertension)
- Coumarin derivatives (such as dicoumarol, acenocoumarol), used to decrease the clotting ability of the blood
- Colesevelam, used to lower cholesterol
- Guanethidine, used to treat high blood pressure (hypertension)
- H2-receptor antagonists used for reducing stomach acid (such as ranitidine) to relieve the symptoms of stomach and duodenal ulcers, to treat the disease where stomach acid rises up into the oesophagus (oesophageal reflux disease), and the Zollinger-Ellison syndrome

Ciclosporin, used to prevent rejection of the transplanted organ
- The toxicity of ciclosporin may increase when taken with Amglidia

Alcohol
- Alcohol may affect the amount of sugar in your blood.

Tell your doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

AMGLIDIA with alcohol

Both acute and chronic alcohol intake may reduce the sugar lowering effect of glibenclamide or dangerously potentiate it by delaying its breakdown in the body. Nausea, vomiting, flushing, dizziness, headache, chest and abdominal discomfort, and general hangover-like symptoms among others have occurred following the concomitant use of alcohol and glibenclamide. Concomitant use of alcohol and glibenclamide should be avoided.

Pregnancy and breast-feeding

This medicine may only be used for the treatment of neonatal diabetes in newborns, infants and children.
This medicine is not intended to be used in pregnant women and patients planning a pregnancy should inform their doctor. It is recommended that such patients change treatment to insulin.
Breast-feeding seems to be compatible, but as a precautious measure monitoring of the fully breast-fed infant's blood sugar level is advisable.

Talk to your doctor about the best way to control your blood sugar in case of pregnancy.

Driving and using machines

Glibenclamide may increase the risk of low blood sugar and therefore have a moderate influence on the ability to drive, to take part in road traffic otherwise or use machines.
You or your child should avoid activities requiring balance (for example, cycling or skateboarding) and driving or using machines if you or your child fee dizzy, tired or unwell.

AMGLIDIA contains sodium
This medicine contains 2.80 mg of sodium per mL, equivalent to 0.1% of the WHO recommended daily intake of 2 g sodium for an adult. To be taken into consideration by patients who have been advised to follow a low salt (sodium) diet.

AMGLIDIA contains benzoate salt
This medicine contains 5 mg benzoate salt in each mL oral suspension. Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

3. How to give AMGLIDIA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dose

Glibenclamide therapy should be started by a doctor experienced in the treatment of patients with very early onset diabetes.

The dose of Amglidia depends on your child's body weight, and will be calculated by the doctor as an amount (volume) in mL oral suspension to be measured with the oral syringe (either an 1 mL or a 5 mL syringe) supplied with the medicine. Your doctor will prescribe the specific pack size and strength including the particular syringe you should use. Do not use any other syringe to administer Amglidia.

It is important you do not adjust yourself the doses of either Amglidia or insulin, unless specifically directed to do so by your child's doctor.

Make sure that you use correct strength of the medicine and the appropriate oral syringe prescribed by your doctor to avoid accidental administration of too high or too low amounts.

The starting dose of Amglidia is 0.2 mg of glibenclamide for each kilogram (kg) of body weight daily, divided in two doses of 0.1 mg/kg. As the dose is increased, it is usually possible to reduce and then stop the dose of insulin the patient is already receiving.

Higher doses of mglidiacan be given as needed and administered in up to four intakes per day based on blood-glucose monitoring, as per titration recommendations given by the referring doctor.

In case of minor vomiting, an antivomiting medicine will be prescribed by your doctor and Amglidia can be continued.
As generally recommended in such situations, if vomiting occurs less than 30 minutes following administration of Amglidia, a new dose can be given. If vomiting occurs more than 30 minutes following administration of Amglidia, no new dose should be given. Always ask your child's doctor for advice in such circumstances.

In case of major vomiting, ketonaemia and ketonuria should be closely monitored by the treating doctor. The doctor may start insulin therapy again, when ketonaemia or ketonuria were found to be responsible for the major vomiting. In case of inability of food or beverage intake, the child should go to emergency department to get an insulin and glucose perfusion until vomiting stops.

Method of administration

Always give the medicine 15 minutes before feeding.

The medicine should be given at the same times each day.

In case of milk feeding, recommendation is given to administer the suspension 15 minutes before child's milk feeding.

This medicine is a ready-for-use oral suspension to be given with a marked oral syringe. Only the oral syringe included in the carton should be used.

The 1 mL syringe is thin and small and graduated in steps of 0.05 mL. The 5 mL syringe is thick and long and graduated in steps of 0.1 mL.

Instructions for use

The dose is measured by drawing the plunger of the syringe back until it reaches the marking for the dose the doctor has prescribed for your child. The dose in mL per administration and the number of administrations per day have to carefully follow the medical prescription.

While the child is awake, position the child in half-sitting position in the hollow of your arm, with the child's head resting on your arm.

Slip about the first 1 cm of the syringe into the child's mouth and place it against the inside cheek; Let the child suck. If the child does not suck, slowly press the plunger of the syringe so that the suspension trickles into the mouth.

Do not lay the child down directly after administration. It is recommended to wait for the child has swallowed the medicine before reverting back to lying position.

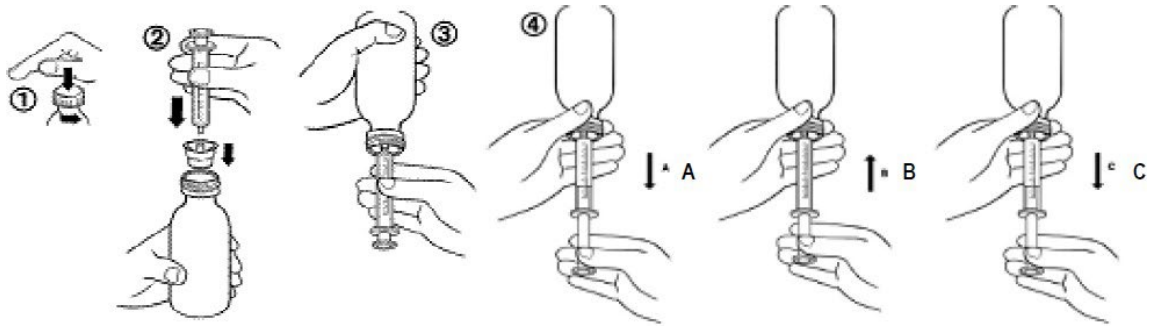
For first use

1. Open the bottle by unscrewing the child-resistant closure while pressing downwards.

2. Insert the adaptor firmly into the bottle while holding the bottle the right way up.
3. Replace the screw cap on the bottle with the adaptor.
4. Retighten the screw cap to push the adaptor well into the bottle.

For each administration

1. The bottle does not need to be shaken before administration. The medicine is administered as a ready-for-use oral suspension to be given using a specific marked syringe.
2. Open the bottle by unscrewing the child-resistant closure while pressing downwards (figure 1).
3. Holding the bottle the right way up, insert the syringe firmly into the adaptor fitted to the bottle (figure 2).
4. Turn the bottle with the syringe upside down (figure 3).
5. Draw back the plunger to obtain the desired volume (figure 4A). Then push the plunger to remove as many air bubbles as possible from the syringe (figure 4B). Finally, draw back the plunger until graduation corresponding to the prescribed dose in ml (figure 4C).
   Note: if air gets into the syringe, empty the syringe into the bottle and start the procedure again.
6. Turn the bottle with the syringe into its upright position.
7. Remove the syringe from the adaptor. Put the syringe into the child mouth and push the plunger to slowly administer the medicine into the mouth.
8. Close the bottle by tightening the screw cap well on top of the adaptor.
   The bottle must be closed after each use and stored for a **maximum of 30 days**.
9. The syringe must be rinsed thoroughly with water, wiped dry after each use and replaced back into the medicine's carton. The oral syringe in the carton should be used only with this medicine.



If you give more AMGLIDIA to your child than you should

See your doctor, nurse or your hospital pharmacist immediately.
There is a risk of hypoglycaemia. You should check capillary blood sugar of your child and follow the instructions described in section 4.

If you forget to give AMGLIDIA

If you forget to give Amglidia, there is a risk of high blood sugar.

You must check your child's blood sugar (capillary blood sugar) and give Amglidia as soon as you

realise you have forgotten to use it. If your child's capillary blood sugar exceeds 3 g/L (or 300 mg/dL or 16.5 mmol/L), check for the presence of ketonuria with a finger stick or urine stick tests according to your child's doctor recommendations. If ketonuria is detected, you must inject insulin immediately according to the procedure defined beforehand with your child's doctor and contact him/her or his/her team for advice.
Do not give a double dose to make up for a forgotten dose.

If you stop giving AMGLIDIA

There is a risk of high blood sugar.

You should check your child's blood sugar (capillary blood sugar). Diabetes symptoms may reappear and may lead to a serious disturbance of the body's metabolism with high blood levels of ketones (ketoacidosis), dehydration and disturbance of the balance of acids in the body. You should therefore never stop the medicine without checking with the doctor looking after your child. Seek advice from your doctor.

You will be requested to bring back remaining Amglidia oral suspension to your doctor at each consultation.

If you have any further questions on the use of this medicine, ask the doctor of your child or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Too low blood sugar (hypoglycaemia) (very common: may affect more than 1 in 10 people)

If you take Amglidia, you are at risk of getting too low blood sugar (hypoglycaemia). The signs of too low blood sugar may include:
- shaking, sweating, feeling very anxious or confused, fast heart beat
- excessive hunger, headache

If your child starts to become pale, sweating, has irregular heart rhythm or seems disoriented, confused or unresponsive, these may be signs that the child's blood sugar is too low ; you should first solve the situation as explained below and you should then talk to your child's doctor to adapt Amglidia's dose.

The risk of low blood sugar is increased if the medicine is not taken with a meal, is taken with alcohol, or if combined with certain medicines(see section 2 Other medicines and Amglidia). Such low blood sugar should be managed by taking sugar by mouth followed by a snack or meal. If very low blood sugar occurs that affects consciousness, emergency services should be called and an intravenous glucose injection performed. After such a severe episode of hypoglycaemia, the child and family should see the child's doctor to check the appropriateness of the dose of glibenclamide suspension.

Eye disorders (common: may affect up to 1 in 10 people):
- Filmy vision in case of high blood glucose levels (hyperglycaemia)

Gastro intestinal disorders (very common: may affect more than 1 in 10 people):

- Transitory diarrhoea
- Abdominal (belly) pain
- Vomiting

- Stomach ache (Dyspepsia)

Teeth problems (common: may affect up to 1 in 10 people):

- Tooth discolouration.

Skin disorders (very common: may affect more than 1 in 10 people):

- Skin rash

Abnormal blood test results (very common: may affect more than 1 in 10 people)

Laboratory blood tests may show changes in blood cells (decrease in white blood cells: neutropenia) and effects on liver function (brief increase in enzymes called transaminases).

Other side effects:

Some other side effects have been observed in adults treated with other medicinal products containing glibenclamide. The following side effects have not been observed with Amglidia.

- Allergic reactions: which may be serious in isolated cases, including difficulties to breath, low blood pressure and shock If your child presents any of these symptoms, you should immediately go to the nearest emergency department
- Skin rash: itching, nettle rash (urticarial), allergic skin reaction, blistering of the skin, skin inflammation.
- Increase in sensitivity of the skin to sunlight
- Transient visual disturbances.
- Other laboratory blood tests changes: increased levels of the white blood cells called eosinophils (hypereosinophilia), mild to severe decrease in blood components called platelets (thrombocytopenia), which can lead to subcutaneous bleeding (purpura).

Tell your doctor or pharmacist if you notice any of the listed side effects:

Reporting of side effects

If you notice any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AMGLIDIA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Keep the bottle the outer carton in order to protect from light.

After first opening, use within 30 days. Keep the bottle tightly closed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information What AMGLIDIA contains

- The active substance is glibenclamide. Each mL contains 0.6 mg glibenclamide.
- The other ingredients are: xanthan gum, hydroxyethylcellulose, lactic acid, purified water, sodium citrate and sodium benzoate (E211) (see section 2 “AMGLIDIA contains sodium and benzoate).

AMGLIDIA looks like and contents of the pack

Amglidia is a white and odourless oral suspension. Each carton contains:
- 1 bottle containing 30 mL oral suspension
- one 1 mL oral syringe (thin and small) and or 5 mL oral syringe (thick and long) depending on the prescribed dose and the volume to be given. The syringe is packed in a transparent bag.
- one syringe adaptor.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the user

AMGLIDIA 6 mg/mL oral suspension
glibenclamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of your child.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AMGLIDIA is and what it is used for

Amglidia contains the active substance called glibenclamide which belongs to a group of medicines called sulphonylureas used for lowering blood sugar (blood-glucose).

Amglidia is used in newborns, infants and children to treat diabetes that occurs at birth (known as neonatal diabetes mellitus). Neonatal diabetes is a disease where the child's body does not release enough insulin to control the level of blood sugar; Amglidia is used only in patients who still have some ability to make insulin.
Sulphonylureas like glibenclamide have been shown to be effective in certain genetic mutations responsible for the genesis of neonatal diabetes.

This medicine is an oral suspension, to be taken by mouth, which is a more convenient treatment for newborns and children compared to regular injections of insulin.

You must talk to a doctor if your child does not feel better or if he/she feels worse after a few days.

2. What you need to know before you give AMGLIDIA Do not give AMGLIDIA

- if your child is allergic to glibenclamide or any of the other ingredients of this medicine (listed in section 6).
- if your child has ketoacidosis (high blood levels of acid substances called ketones).
- if your child suffers from porphyria (inability to break down body chemicals called porphyrins).
- if your child is treated with bosentan, e.g. a medicine used to treat problems of blood circulation.
- if your child suffers from severe renal dysfunction.
- if your child suffers from severe liver dysfunction.

Warnings and precautions

Talk to your doctor before your child is given Amglidia.

Your child's blood sugar levels may become too low (hypoglycaemia) after taking Amglidia. Tell the doctor if your child is pale, sweating, has irregular heart rhythm or seems disoriented, confused or unresponsive. See also section 4. Too low blood sugar (hypoglycaemia).

Ask your doctor to determine at which frequency capillary blood sugar should be checked.

G6PD is an enzyme evolved in sugar metabolism. If your child carries a G6PD enzyme deficiency, he/she may experiment an abnormal breakdown of red blood cells (acute haemolytic anaemia) after taking Amglidia.
Tell the doctor if you know that your child is affected by G6PD deficiency and contact him/her if you notice that your child is pale as compared to usually.

Tell your doctor if your child suffers from renal or liver disorders.

Your child may experience diarrhoea when the dose of glibenclamide suspension is increased but it will be transitory if the dose is maintained.
Your child may experience nausea. If your child is able to take the glibenclamide suspension, do not stop the treatment.
Talk to your doctor if your child experienced vomiting, the doctor may decide to treat your child with insulin until vomiting stops in case of major vomiting.
The doctor may also decide to treat your child with an anti-vomiting medicine in case of minor vomiting. In this case, Amglidia will be continue.

Children and adolescents

Amglidia is to be used for newborns, infants and children.

Other medicines and AMGLIDIA

Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines as some medicines while taking Amglidia may give more side effects or affect the way Amglidia is working.

It is especially important to inform your child's doctor or pharmacist of the following:

These medicines may decrease the amount of sugar in your blood when taken with Amglidia:
- ACE inhibitors (such as captopril and enalapril), used to treat high blood pressure (hypertension),
- Anabolic steroids and male sex hormones (such as testosterone enanthate), used to treat low testosterone levels (testosterone deficiency)
- Biguanides (such as metformin), used to treat diabetes mellitus
- Chloramphenicol (taken by mouth), an antibiotic used to treat infections
- Clarithromycin, an antibiotic used to treat certain infections
- Cyclophosphamides, used to treat different types of cancer
- Disopyramide, used to treat an irregularity in the heart beat
- Fibrates (such as bezafibrate, fenofibrate, gemfibrozil), used to lower the level of fats
- Fluoxetine, used to treat depression and anxiety disorders
- Heparin, used to decrease the clotting ability of the blood
- Ifosfamide, used to treat different types of cancers
- Insulin, used to lower the amount of sugar in the blood (blood sugar level)
- MAO inhibitors (such as iproniazide), used to treat depression
- Miconazole, used to treat fungal infection
- Other oral antidiabetics (such as metformin), used to lower the amount of sugar in the blood (blood-glucose level)
- Oxypentifylline, used to improve blood flow in the extremities (peripheral blood flow)
- Probenecid, used to treat gout, gouty arthritis

- Quinolone antibiotics (such as nalidixic acid and ciprofloxacine), used to treat infections
- Sulfamethoxazole with trimethoprim (Co-trimoxazole), used to treat infections
- Salicylates (such as aminosalicylic acid, para-aminosalicylic acid), used for tuberculosis
- Tetracycline antibiotics (such as doxycycline and minocycline), used to treat infections

These medicines may increase the amount of sugar in your blood when taken with Amglidia:
- Acetazolamide, used to treat damage to the nerve in the eye (glaucoma)
- Adrenaline (epinephrine and other sympathomimetic agents), used to treat serious allergic reaction, the abrupt loss of heart beat (cardiovascular arrest), asthma
- Barbiturates (such as phenobarbital), used to treat epilepsy
- Calcium channel blockers (such as nifedipine), used to treat high blood pressure
- Cimetidine, used to relieve the symptoms of stomach and duodenal ulcers, to treat the disease where stomach acid rises up into the oesophagus (oesophageal reflux disease), and to treat the Zollinger-Ellison syndrome
- Corticosteroids (such as prednisone, prednisolone), used in various indications such as inflammation and asthma
- Diazoxide, used for low blood sugar
- Diuretics (such as furosemide, hydrochlorothiazide), used to treat high blood pressure in the arteries (arterial hypertension)
- Glucagon, used to treat high amounts of sugar in the blood (high blood-glucose level)
- Isoniazid, used to treat tuberculosis
- Large doses of laxatives (such as macrogol)
- Nicotinic acid (in high doses), used to decrease high levels of cholesterol and triglycerides which are fat-like substances in the blood
- Oestrogens (such as 17-beta oestradiol), used for hormonal treatment
- Phenothiazine derivatives (such as chlorpromazine), used to treat schizophrenia and other psychoses
- Phenytoin, used to treat epilepsy
- Progestogens (such as desogestrel, dydrogesterone), used for hormonal treatment
- Rifampicin, used to treat infections including tuberculosis
- Thyroid hormones (such as L-thyroxin), used for hormonal treatment

These medicines may decrease the amount of sugar in your blood or may hide low sugar levels when taken with Amglidia
- Beta-receptor blockers (such as propranolol), used to treat high blood pressure (hypertension), to control irregular or fast heart beats, or to help prevent additional heart attack

These medicines may affect the amount of sugar in your blood (either increase, decrease or both) and/or the control of sugar in plasma when taken with Amglidia
- Bosentan, used to treat high blood pressure (hypertension) in the blood vessels between the heart and the lungs.
- Clonidine, used to treat high blood pressure in the arteries (arterial hypertension)
- Coumarin derivatives (such as dicoumarol, acenocoumarol), used to decrease the clotting ability of the blood
- Colesevelam, used to lower cholesterol
- Guanethidine, used to treat high blood pressure (hypertension)
- H2-receptor antagonists used for reducing stomach acid (such as ranitidine) to relieve the symptoms of stomach and duodenal ulcers, to treat the disease where stomach acid rises up into the oesophagus (oesophageal reflux disease), and the Zollinger-Ellison syndrome

Ciclosporin, used to prevent rejection of the transplanted organ.
- The toxicity of ciclosporin may increase when taken with Amglidia

Alcohol
- Alcohol may affect the amount of sugar in your blood.

Tell your doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

AMGLIDIA with alcohol

Both acute and chronic alcohol intake may reduce the sugar lowering effect of glibenclamide or dangerously potentiate it by delaying its breakdown in the body. Nausea, vomiting, flushing, dizziness, headache, chest and abdominal discomfort, and general hangover-like symptoms among others have occurred following the concomitant use of alcohol and glibenclamide. Concomitant use of alcohol and glibenclamide should be avoided.

Pregnancy and breast-feeding

This medicine may only be used for the treatment of neonatal diabetes in newborns, infants and children.
This medicine is not intended to be used in pregnant women and patients planning a pregnancy should inform their doctor. It is recommended that such patients change treatment to insulin.
Breast-feeding seems to be compatible, but as a precautious measure monitoring of the fully breast-fed infant's blood sugar level is advisable.

Talk to your doctor about the best way to control your blood sugar in case of pregnancy.

Driving and using machines

Glibenclamide may increase the risk of low blood sugar and therefore have a moderate influence on the ability to drive, to take part in road traffic otherwise or use machines.
You or your child should avoid activities requiring balance (for example, cycling or skateboarding) and driving or using machines if you or your child fee dizzy, tired, or unwell.

AMGLIDIA contains sodium

This medicine contains 2.80 mg of sodium per mL, equivalent to 0.1% of the WHO recommended daily intake of 2 g sodium for an adult. To be taken into consideration by patients who have been advised to follow a low salt (sodium) diet.

AMGLIDIA contains benzoate salt

This medicine contains 5 mg benzoate salt in each mL oral suspension. Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

3. How to give AMGLIDIA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dose

Glibenclamide therapy should be started by a doctor experienced in the treatment of patients with very early onset diabetes.

The dose of Amglidia depends on your child's body weight, and will be calculated by the doctor as an amount (volume) in mL of oral suspension to be measured with the oral syringe (either an 1 mL or a 5 mL syringe) supplied with the medicine. Your doctor will prescribe the specific pack size and strength including the particular syringe you should use. Do not use any other syringe to administer Amglidia.

It is important you do not adjust yourself the doses of either Amglidia or insulin, unless specifically directed to do so by your child's doctor.

Make sure that you use correct strength of the medicine and the appropriate oral syringe prescribed by your doctor to avoid accidental administration of too high or too low amounts.

The starting dose of Amglidia is 0.2 mg of glibenclamide for each kilogram (kg) of body weight daily, divided in two doses of 0.1 mg/kg. As the dose is increased, it is usually possible to reduce and then stop the dose of insulin the patient is already receiving.

Higher doses of Amglidia can be given as needed and administered in up to four intakes per day, based on blood-glucose monitoring, as per titration recommendations given by the referring doctor.

In case of minor vomiting, an antivomiting medicine will be prescribed by your doctor and Amglidia can be continued.
As generally recommended in such situations, if vomiting occurs less than 30 minutes following administration of Amglidia, a new dose can be given. If vomiting occurs more than 30 minutes following administration of Amglidia, no new dose should be given. Always ask your child's doctor for advice in such circumstances.

In case of major vomiting, ketonaemia and ketonuria should be closely monitored by the treating doctor. The doctor may start insulin therapy again, when ketonaemia or ketonuria were found to be responsible for the major vomiting. In case of inability of food or beverage intake, the child should go to emergency department to get an insulin and glucose perfusion until vomiting stops.

Method of administration

Always give the medicine before feeding.

The medicine should be given at the same time each day.

In case of milk feeding, recommendation is given to administer the suspension 15 minutes before child's milk feeding.

This medicine is a ready-for-use oral suspension to be given with a marked oral syringe. Only the oral syringe included in the carton should be used.
The 1 mL syringe is thin and small and graduated in steps of 0.05 mL. The 5 mL syringe is thick and long and graduated in steps of 0.1 mL.

Instructions for use

The dose is measured by drawing the plunger of the syringe back until it reaches the marking for the dose the doctor has prescribed for your child. The dose in mL per administration and the number of administrations per day have to carefully follow the medical prescription.

While the child is awake, position the child in half-sitting position in the hollow of your arm, with the child's head resting on your arm.

Slip about the first 1 cm of the syringe into the child's mouth and place it against the inside cheek; Let the child suck. If the child does not suck, slowly press the plunger of the syringe so that the suspension trickles into the mouth.

Do not lay the child down directly after administration. It is recommended to wait for the child has swallowed the medicine before reverting back to lying position.

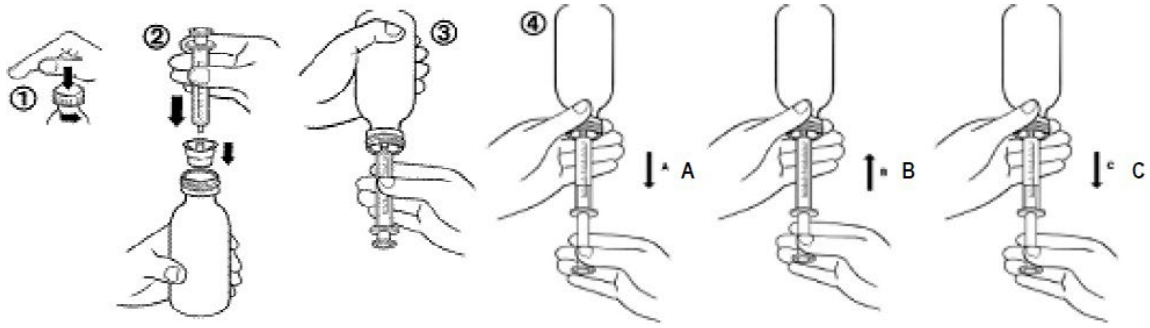
For first use

1. Open the bottle by unscrewing the child-resistant closure while pressing downwards.

2. Insert the adaptor firmly into the bottle while holding the bottle the right way up.
3. Replace the screw cap on the bottle with the adaptor.
4. Retighten the screw cap to push the adaptor well into the bottle.

For each administration

1. The bottle does not need to be shaken before administration. The medicine is administered as a ready-for-use oral suspension to be given using a specific marked syringe.
2. Open the bottle by unscrewing the child-resistant closure while pressing downwards (figure 1).
3. Holding the bottle the right way up, insert the syringe firmly into the adaptor fitted to the bottle (figure 2).
4. Turn the bottle with the syringe upside down (figure 3).
5. Draw back the plunger to obtain the desired volume (figure 4A). Then push the plunger to remove as many air bubbles as possible from the syringe (figure 4B). Finally, draw back the plunger until graduation corresponding to the prescribed dose in mL (figure 4C).
   Note: if air gets into the syringe, empty the syringe into the bottle and start the procedure again.
6. Turn the bottle with the syringe into its upright position.
7. Remove the syringe from the adaptor. Put the syringe into the child mouth and push the plunger to slowly administer the medicine into the mouth.
8. Close the bottle by tightening the screw cap well on top of the adaptor.
   The bottle must be closed after each use and stored for a **maximum of 30 days**.
9. The syringe must be rinsed thoroughly with water, wiped dry after each use and replaced back into the medicine's carton. The oral syringe in the carton should be used only with this medicine.



If you give more AMGLIDIA to your child than you should
See your doctor, nurse or your hospital pharmacist immediately.

There is a risk of hypoglycaemia. You should check capillary blood sugar of your child and follow the instructions described in section 4.

If you forget to give AMGLIDIA

If you forget to give Amglidia, there is a risk of high blood sugar.

You must check your child's blood sugar (capillary blood sugar) and give Amglidia as soon as you realise you have forgotten to use it. If your child's capillary blood sugar exceeds 3 g/L (or 300 mg/dL

or 16.5 mmol/L), check for the presence of ketonuria with a finger stick or urine stick tests according to your child's doctor recommendations. If ketonuria is detected, you must inject insulin immediately according to the procedure defined beforehand with your child's doctor and contact him/her or his/her team for advice.

Do not give a double dose to make up for a forgotten dose.

If you stop giving AMGLIDIA

There is a risk of high blood sugar.

You should check your child's blood sugar (capillary blood sugar). Diabetes symptoms may reappear and may lead to a serious disturbance of the body's metabolism with high blood levels of ketones (ketoacidosis), dehydration and disturbance of the balance of acids in the body. You should therefore never stop the medicine without checking with the doctor looking after your child. Seek advice from your doctor.

You will be requested to bring back remaining Amglidia oral suspension to your doctor at each consultation.

If you have any further questions on the use of this medicine, ask the doctor of your child or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Too low blood sugar (hypoglycaemia) (very common: may affect more than 1 in 10 people)
If you take Amglidia, you are at risk of getting too low blood sugar (hypoglycaemia). The signs of too low blood sugar may include:
- shaking, sweating, feeling very anxious or confused, fast heart beat
- excessive hunger, headache

If your child starts to become pale, sweating, has irregular heart rhythm or seems disoriented, confused or unresponsive, these may be signs that the child's blood sugar is too low; you should first solve the situation as explained below and you should then talk to your child's doctor to adapt Amglidia's dose.

The risk of low blood sugar is increased if the medicine is not taken with a meal, is taken with alcohol, or if combined with certain medicines (see section 2 Other medicines and Amglidia). Such low blood sugar should be managed by taking sugar by mouth followed by a snack or meal. If very low blood sugar occurs that affects consciousness, emergency services should be called and an intravenous glucose injection performed. After such a severe episode of hypoglycaemia, the child and family should see the child's doctor to check the appropriateness of the dose of glibenclamide suspension.

Eye disorders (common: may affect up to 1 in 10 people)

- Filmy vision in case of high blood glucose levels (hyperglycaemia)

Gastro intestinal disorders (very common: may affect more than 1 in 10 people)

- Transitory diarrhoea
- Abdominal (belly) pain
- Vomiting
- Stomach ache (Dyspepsia)

Teeth problems (common: may affect up to 1 in 10 people)

- Tooth discolouration.

Skin disorders (very common: may affect more than 1 in 10 people)

- Skin rash

Abnormal blood test results (very common: may affect more than 1 in 10 people)

Laboratory blood tests may show changes in blood cells (decrease in white blood cells: neutropenia) and effects on liver function (brief increase in enzymes called transaminases).

Other side effects:

Some other side effects have been observed in adults treated with other medicinal products containing glibenclamide. The following side effects have not been observed with Amglidia.

- Allergic reactions: which may be serious in isolated cases, including difficulties to breath, low blood pressure and shock. If your child presents any of these symptoms, you should immediately go to the nearest emergency department.
- Skin rash: itching, nettle rash (urticarial), allergic skin reaction, blistering of the skin, skin inflammation.
- Increase in sensitivity of the skin to sunlight.
- Transient visual disturbances.
- Other laboratory blood tests changes: increased levels of the white blood cells called eosinophils (hypereosinophilia), mild to severe decrease in blood components called platelets (thrombocytopenia) which can lead to subcutaneous bleeding (purpura).

Tell your doctor or pharmacist if you notice any of the listed side effects:

Reporting of side effects

If you notice any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store AMGLIDIA

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
Keep the bottle in the outer carton in order to protect from light.

After first opening, use within 30 days. Keep the bottle tightly closed.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information What AMGLIDIA contains

- The active substance is glibenclamide. Each mL contains 6 mg glibenclamide.
- The other ingredients are: xanthan gum, hydroxyethylcellulose, lactic acid, purified water sodium citrate and sodium benzoate (E211) (see section 2 “AMGLIDIA contains sodium

and benzoate").

What AMGLIDIA looks like and contents of the pack

Amglidia is a white and odourless oral suspension. Each carton contains:

- 1 bottle containing 30 mL oral suspension
- one 1 mL oral syringe (thin and small) or one 5 mL oral syringe (thick and long) depending on the prescribed dose and the volume to be given. The syringe is packed in a transparent bag.
- one syringe adaptor.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Make sure that you use correct strength of the medicine and the appropriate oral syringe prescribed by your doctor to avoid accidental administration of too high or too low amounts.