SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

AMGLIDIA 0.6 mg/mL oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMGLIDIA 0.6 mg/mL oral suspension

Each mL contains 0.6 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 5mL) 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.

<u>Outpatient treatment introduction</u>

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 exceeds16.5 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 treat 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 dosage adjustment of ciclosporin is 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.

A summary of the interactions detailed above and further interactions are summarised 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 by delaying its metabolic inactivation	Incorrect control of plasma glucose
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	Incorrect control of plasma glucose

	effect	
	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 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
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 microgram/L for a lower limit of normal of 1.5×10^3/ microgram/L).
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 Yellow Card Scheme in UK Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 0.5 mg/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 (Cmax) 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

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

Distributed by:

Bioprojet UK Limited,
Unit B, Stanley Court,
3 Glenmore Business Park,
Telford Road,
Salisbury SP2 7GH,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 50687/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/11/2024

10 DATE OF REVISION OF THE TEXT

20/01/2025