24 May 2018
EMA/172099/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Amglidia (glibenclamide)
Treatment of neonatal diabetes
EU/3/15/1589 (EMA/OD/149/15)
Sponsor: AMMTeK

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Glibenclamide
International Non-Proprietary Name	Glibenclamide
Orphan indication	Treatment of neonatal diabetes
Pharmaceutical form	Oral suspension
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	A10BB01
Sponsor's details:	AMMTeK 15 rue Béranger 75003 Paris France
Orphan medicinal product designation procedural history	
Sponsor/applicant	AMMTeK
COMP opinion date	12 November 2015
EC decision date	15 January 2016
EC registration number	EU/3/15/1589
Post-designation procedural history	
Transfer of sponsorship	Transfer from AMMTeK to Pharma Services - EC decision of 27 September 2016
	2nd transfer from Pharma Services to AMMTeK - EC decision of 10 February 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	M. Weise, A. Gyurasics
Applicant	AMMTeK
Application submission date	6 October 2016
Procedure start date	27 October 2016
Procedure number	EMA/H/C/004379
Invented name	Amglidia
Therapeutic indication	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 Further information on Amglidia can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	22 February 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	F. Nauman-Winter, K. Westermark
Sponsor's report submission date	6 October 2016
COMP discussion	5-7 December 2017

COMP opinion date	27 February 2018

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing glibenclamide was considered justified based on preliminary data in paediatric patients with the condition showing improved glycaemic control without increasing hypoglycaemia risk;
- the condition is life-threatening and chronically debilitating due to hyperglycemia which include symptoms such as thirst, frequent urination, and dehydration. In severe cases this is associated with ketoacidosis which can led to death;
- the condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that when glibenclamide is used in the treatment of patients with neonatal diabetes there is a reduction or elimination of the use of insulin. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Neonatal diabetes mellitus (NDM) is a rare form of diabetes characterized by hyperglycemia occurring in the first few months of life. It can present as either transient NDM (TNDM), which resolves by a few months, or permanent NDM (PNDM), which continues throughout life. The etiology of this disease remained unclear until recently, when advances in molecular genetic techniques illuminated the mechanisms involved in the pathogenesis of the disease. While most TNDM cases are caused by the overexpression of chromosome 6q24, the majority of PNDM cases are due to mutations in the adenosine triphosphate-sensitive potassium (KATP) channel. (Research and Reports in Neonatology 2014:4 55–64). The condition is well described in the literature which clearly differentiates it from Type 1 and Type 2 diabetes linking the condition to a dysfunctioning of the beta cell due to a specific gene mutation. The aetiology of the condition is therefore different from the more commonly diagnosed forms of diabetes.

The COMP designated this condition as a distinct medical entity.

The approved therapeutic indication “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." falls within the scope of the designated orphan indication "neonatal diabetes".

Intention to diagnose, prevent or treat

Based on the CHMP assessment the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

Symptoms of Neonatal diabetes include thirst, frequent urination, and dehydration. NDM can be diagnosed by finding elevated levels of glucose in blood or urine. In severe cases, the deficiency of insulin may cause the body to produce an excess of acid, resulting in a potentially life-threatening condition called ketoacidosis.

Number of people affected or at risk

The sponsor has provided a literature search covering 5 publications ranging from 1999 to 2012. Of these 5 publications only 4 were considered as the one from Bappal et al from 1999 was based on data from Oman which although supportive does not directly reflect data collected in Europe as the incidence reported in Oman is 1 in 45,000 and is one of the highest in the world. The other four publications where based on data collected in Germany, Austria, Italy, Slovakia, UK, the Netherlands and Poland. The sponsor highlighted that few publications exist on the prevalence of NDM and that they describe transient and permanent forms of neonatal diabetes each representing half of the reported cases. Transients cases have been reported to last up to 6 months from birth, permanent cases may last longer with some reports stating they may go into adulthood. Many transient forms have been linked to mutations of ABCC8 while permanent forms to mutations of KCNJ11 (although some transient forms have been associated with this mutation).

The data used in the 4 publications are derived from:

- A large representative database for paediatric diabetes patients in Germany and Austria (Grulich-Henn, 2010). Based on the continuous diabetes data acquisition system for prospective surveillance, which includes 51,587 patients with onset of diabetes before the age of 18 years from 299 centres in Germany and Austria.
- Iafusco et al in 2012 reported reviewing patients referred to the Italian reference laboratory for neonatal diabetes between years 2005 and 2010 and screened for mutations in common NDM genes (KCNJ11 , ABCC8 , and INS) and for uniparental isodisomy of chromosome 6 (UDP6). A questionnaire aimed at identifying ND cases investigated in other laboratories was sent to 54 Italian reference centres for paediatric diabetes.
- A Slovakian team having reviewed the Slovak Children Diabetes Registry to find NDM patients (Stanik, 2007).
- Slingerland et al 2009 report data obtained from the Exeter Peninsula Molecular Genetics Laboratory based at the Royal Devon and Exeter Hospital (Exeter, UK) which began recruiting patients worldwide prior to the discovery reported in 2004 that KCNJ11 mutations are the most common cause of NDM. The highest referral rates are in the UK, the Netherlands and Poland, where there have been considerable educational initiatives to inform clinicians of the free-of-charge diagnostic service.

The sponsor derives from these publications that the highest reported incidence of neonatal diabetes is 1 in 90,000 with the lowest reported incidence being 1 in 260,000 for the KCNJ11 mutation which is

the most common type reported by Slingerland et al. The highest reported incidence is still half of the reported incidence in Oman which is 1 in 45,000.

The sponsor then makes an assumption of the population of the 59 children born each year with the condition will make it to 18 years of age. They mix "transient" and "permanent" forms in these 59 children born each and assume all will survive to the age of 18 years. From this they establish that 1062 patients could represent the highest point prevalence for all the mutations associated with the condition whether they are clinically manifesting or not. The 1062 patients were then divided by the total population of the European Union which they propose to be 512 million in 2016. A prevalence of 0.02 in 10,000 was then proposed which was accepted by the COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

At the time of designation the COMP was of the opinion that insulin was indicated for use in this condition although it was acknowledged that the SmPCs do not specifically identify the condition in the wording of the indication. As this form of diabetes occurs within the first 6 months of life and insulin is the only product authorised for use in children it was considered that the indication of insulin in section 4.1 of the SmPC for Humalog which states: "*For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Insulin is also indicated for the initial stabilisation of diabetes mellitus*." and Section 4.2 which covers posology and the population to be treated states: "*Paediatric population Humalog can be used in adolescents and children*" would cover this population. The COMP was of the opinion that an indication for "diabetes mellitus" would cover the term neonatal diabetes mellitus.

The use of glibenclamide and other sulphylureas is specifically contraindicated for use in the paediatric population. Section 4.2 of the SmPC for glibenclamide for example states that: "*Children: Glibenclamide is not recommended for use in children".* This contraindication in children is also found for other sulphonylureas.

Significant benefit

The marketing authorisation application to the CHMP is based on well-established use.

To support the significant benefit the sponsor used the same bibliographic data used at the time of orphan designation. Indeed, the submission for the market authorisation includes this same publication which is based on work done by the sponsor. Two articles are of interest for the purpose of understanding the impact of using a sulphonylurea in the treatment of this condition on top of insulin use. Both articles were published in the New England Journal of Medicine (Babenko et al N Engl J Med 2006;355:456-66 and Pearson et al N Engl J Med 2006;355:467-77).

Babenko et al describes the use of glibenclamide in a section of patients which make up a cohort of 34 patients who were treated with either glibenclamide or glipizide. In the article the authors describe first the identification of patients with a specific mutation for this condition. The patients were on insulin at the time of inclusion and were given glibenclamide. The efficacy of glibenclamide was measured based on glucose levels and insulin was discontinued when satisfactory metabolic control was achieved. The authors' state in this paper: "*Initial insulin treatment was required for 1, 2.5, 3, 4, 4, 8.5, and 10*

months in probands with transient neonatal diabetes in Families 16, 34, 17, 19, 13, 36, and 28, respectively. The last documented dose of insulin varied from 0.12 to 1.2 U per kilogram per day, with a mean of 0.67 U per kilogram per day. After identification of the mutations in the patients with permanent neonatal diabetes, glyburide (also known as glibenclamide) therapy was initiated and found to be successful and insulin was discontinued after 2 days in the proband from Family 12 and after 15 days in the proband from Family 16. The current doses of glyburide are 0.59 and 0.22 mg per kilogram per day, respectively."

In Pearson et al the authors report that they assessed glycaemic control in 49 consecutive neonatal diabetes patients with Kir6.2 mutations who received appropriate doses of sulfonylureas. In the result section the authors report: "*A total of 44 patients (90 percent) successfully discontinued insulin after receiving sulfonylureas. The extent of the tolbutamide blockade of KATP channels in vitro reflected the response seen in patients. Glycated hemoglobin levels improved in all patients who switched to sulfonylurea therapy (from 8.1 percent before treatment to 6.4 percent after 12 weeks of treatment, P<0.001). Improved glycemic control was sustained at one year. Sulfonylurea treatment increased insulin secretion, which was more highly stimulated by oral glucose or a mixed meal than by intravenous glucose. Exogenous glucagon increased insulin secretion only in the presence of sulfonylureas".*

The COMP noted a third study published in 2015 by Beltrand et al, (GlidKir study). In this study, which included 19 patients diagnosed with this condition, patients were switched from insulin to a sulphonylurea. The authors of this paper report: "*At baseline, hypotonia, deficiencies in gesture conception or realization, and attention disorders were common. SU improved HbA1c levels (median change 21.55% [range 23.8 to 0.1]; P < 0.0001), intelligence scores, hypotonia (in 12 of15 patients), visual attention deficits (in 10 of 13 patients), gross and fine motor skills (in all patients younger than 4 years old), and gesture conception and realization (in 5 of 8 older patients). Electrophysiological muscle and nerve tests were normal. Cerebral MRI at baseline showed lesions in 12 patients, suggesting that the impairments were central in origin."* This third paper further substantiates the findings of the earlier two papers cited by the sponsor.

All three papers show that the use of glibenclamide can reduce and eliminate the use of insulin and improve the metabolic control (HbA_{1c}). This was shown in patients with both the transient and permanent forms of the condition. This can be considered as a clinically relevant advantage in the treatment of patients with the condition.

4. COMP position adopted on 27 February 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of neonatal diabetes (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 0.02 in 10,000 persons in the European Union, at the time of the review of the designation criteria;the condition is life-threatening and chronically debilitating due to hyperglycemia which include symptoms such as thirst, frequent urination, and dehydration. In severe cases this is associated with ketoacidosis which can lead to death;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Amglidia may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data that demonstrate that when the age appropriate formulation of glibenclamide is used in the treatment of patients with neonatal diabetes, their metabolic control is improved and the need to use insulin is reduced or eliminated.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Amglidia, glibenclamide, EU/3/15/1589 for treatment of neonatal diabetes is not removed from the Community Register of Orphan Medicinal Products.