22 February 2018
EMA/153558/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Amglidia

International non-proprietary name: glibenclamide

Procedure No. EMEA/H/C/004379/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Amglidia
Applicant:	Ammtek 15, rue Beranger 75003 Paris FRANCE
Active substance:	GLIBENCLAMIDE
International Nonproprietary Name:	glibenclamide
Pharmaco-therapeutic group (ATC Code):	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS, Sulfonylureas (A10BB01)
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.
Pharmaceutical form	Oral suspension
Strengths:	0.6 mg/ml and 6 mg/ml
Route of administration:	Oral use
Packaging:	bottle (glass)
Package size(s):	1 bottle + 1 bottle adapter + one oral syringe (1ml or 5ml)

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List of abbreviations

6q24	a gene locus associated with neonatal diabetes mellitus
ABCC8	gene encoding SUR1
CEP	Certificate of Suitability of the EP
DAD	Diode-Array Detection
DCD	Developmental coordination disorder
DEND	Developmental delay, Epilepsy and Neonatal Diabetes
EDQM	European Directorate for the Quality of Medicines
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iDEND	intermediate DEND
IDDM	insulin dependent diabetes mellitus
IR	Infrared
IUGR	Intrauterine growth restriction
KATP channel	ATP-sensitive potassium channel
KCNJ11	gene encoding Kir6.2
Kir6.2	Potassium inward rectifier 6.2
MRI	Magnetic resonance imaging
NEJM	The New England Journal of Medicine
ND	Neonatal Diabetes
NDM	Neonatal Diabetes mellitus
NSH	neonatal syndromic hyperglycaemia
PDCO	Paediatric Committee
Ph. Eur.	European Pharmacopoeia
PIP	paediatric investigation plan
PND	Permanent ND
PNDM	Permanent NDM

PNSH	Permanent neonatal syndromic hyperglycaemia
PNIDDM	permanent IDDM of neonatal onset
PP	Polypropylene
PSD	Particle size distribution
SU	Sulfonylurea
SUR1	Sulfonylurea receptor 1
TLC	Thin layer chromatography
TND	Transient ND
TNDM	Transient NDM
TNSH	Transient neonatal syndromic hyperglycaemia
UV	Ultraviolet
XRD	X-Ray Diffraction
XRPD	X-Ray Power Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pharma Services submitted on 6 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Amglidia, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The application was transferred from Pharma Services to Ammtek during the submission of responses to the CHMP consolidated List of Questions on 20 April 2017. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 January 2016.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3)of Directive 2001/83/EC.

The applicant applied for the following indication (wording at submission):

“Amglidia is a hypoglycaemic agent indicated for the oral treatment of neonatal diabetes, for use in newborns, infants and children.”

Amglidia was designated as an orphan medicinal product EU/3/15/1589 on 15 January 2016. Amglidia was designated as an orphan medicinal product in the following indication: treatment of neonatal diabetes.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Amglidia as an orphan medicinal product in the approved indication. More information on the COMP’s review can be found in the Orphan maintenance assessment report published under the ‘Assessment history’ tab on the Agency’s website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Daonil and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: DAONIL 5mg Tablets
- Marketing authorisation holder: Sanofi
- Date of authorisation: 01-01-1969
- Marketing authorisation granted by:
  - Member State (EEA) : France
    - National procedure
- Marketing authorisation number: 3400930281055

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: DAONIL 5mg Tablets
- Marketing authorisation holder: Sanofi
- Date of authorisation: (01-01-1969)
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
- Marketing authorisation number: 3400930281055

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: DAONIL 5mg Tablets
- Marketing authorisation holder: Sanofi
- Date of authorisation: (01-01-1969)
- Marketing authorisation granted by:
  - Member State (EEA): France
    - National procedure
  - Marketing authorisation number(s): 3400930281055
- Bioavailability study number: 1AMK1 /Glibentek1

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant did not seek protocol assistance at the CHMP.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 6 October 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 26 May 2016. The procedure reverted to standard TT at the time of the adoption of the List of Questions.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 24 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 03 January 2017.
- During the meeting on 12 January 2017 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 24 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 April 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 May 2017.
- During the PRAC meeting on 09 June 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 10 November 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 29 November 2017.
- The Rapporteur circulated updated Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 7 December 2017.
- During the CHMP meeting on 14 December 2017, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the second CHMP consolidated List of Outstanding Issues on 17 January 2018.

- The Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the second List of outstanding issues to all CHMP members on 7 February 2018.
- The Rapporteur circulated updated CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the second List of outstanding issues to all CHMP members on 12 February 2018.
- During the meeting on 19-22 February 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Amglidia on 22 February 2017.

2. Scientific discussion

2.1. Introduction

Neonatal diabetes is a disease of early infancy due to mutations in the genes coding for the Kir6.2 and SUR1 subunits of the pancreatic β-cell ATP-sensitive potassium channel which result in failure of insulin secretion.

The prevalence of neonatal diabetes is less than 0.02 per 10,000 individuals in the EU and should be considered as an extremely rare disorder of genetic origin which cannot be prevented.

Neonatal diabetes is a detectable condition that needs most often emergency treatment with IV fluid and insulin, the only method so far to re-establish metabolic control, and to avoid short-term risks such a ketoacidosis, dehydration and death in newborns and toddlers.

Genetic testing for mutations in the genes coding for the Kir6.2 and SUR1 subunits of the pancreatic beta-cell ATP-sensitive potassium channel remains mandatory for diagnosis of all suspected cases of neonatal diabetes.

The proof of concept to use Glibenclamide oral suspension for newborns, infants and children for the treatment of neonatal diabetes has been established in two studies reported in 2006 (Pearson et al. NEJM, 2006 and Babenko et al. NEJM, 2006).

The conclusion of one of the articles (Pearson et al. NEJM, 2006) was that "Sulphonylurea therapy is safe in the short term for patients with diabetes caused by KCNJ11 mutations and is probably more effective than insulin therapy. This pharmacogenetic response to sulphonylureas may result from the closing of mutant KATP channels, thereby increasing insulin secretion in response to incretins and glucose metabolism."

The conclusion of the second article (Babenko et al. NEJM, 2006) was that "Dominant mutations in ABCC8 accounted for 12 percent of cases of neonatal diabetes in the study group. Diabetes results from a newly discovered mechanism whereby the basal magnesium-nucleotide-dependent stimulatory action of SUR1 on the Kir pore is elevated and blockade by sulphonylureas is preserved."

It is therefore possible to switch from insulin injections to oral glibenclamide and to treat neonatal diabetes associated with an insulin secretion defect of pancreatic β-cells provided that there are insulin secreting β-cells in the endocrine pancreas.

Glibenclamide is an antidiabetic drug in a class of medications known as sulfonylureas and is currently approved for the treatment of adult patients with type 2 diabetes. In clinical practice, sulfonylureas like glibenclamide are administered off label, or within clinical research protocols, to treat neonatal diabetes in newborns/children, using commercially available glibenclamide tablets licensed for adults only.

To render glibenclamide tablets suitable for oral intake by newborns/children, the nursing staff, under medical prescription, or the parents at home, must crush the tablet into small pieces and present the drug to the infant by mixing the fragments with a small volume of water; the mixture is then administered with an oral syringe. The use of such formulation is not ideal as it is rather inaccurate and can lead to errors in administration in new-borns and infants.

To overcome the obvious inconvenience of this process and in view of a better compliance, as no specific oral glibenclamide formulation is available for the paediatric population, AMMTeK has developed an oral

glibenclamide suspension presented in two strengths (0.6 mg/ml and 6 mg/ml), adapted to be used in newborns, infants up to 23 months and children to replace crushed tablets of glibenclamide previously used off-label and long-term use of insulin, where possible for the treatment of neonatal diabetes.

The development programme in support of the efficacy and safety of Amglidia 0.6 mg/ml and 6 mg/ml, oral suspension is based on both bibliographical data and data from clinical studies conducted by the applicant and includes:

- two proof of concept studies (Babenko et al. NEJM, 2006 and Pearson et al. NEJM, 2006) in which sulfonylureas were used off-label in patients with neonatal diabetes.

- a prospective, open-label, single-center, single arm, non-randomized, uncontrolled phase II study (GlidKir study, ClinicalTrials.gov Identifier: NCT00610038) of glibenclamide crushed Daonil® tablets including pharmacokinetic data; 19 patients with neonatal diabetes (age 0.1–18.5 years) were enrolled and 18 patients switched from insulin to SU therapy to examine improvement of neuropsychological functioning (Beltrand et al. Diabetes Care, 2015).

- a bioavailability study (1AMK1/Glibentek1) comparing pharmacokinetics of glibenclamide crushed tablets versus glibenclamide oral suspension in healthy volunteers (Clinical study report, 2012).

- a Phase II, single-centre, prospective, open-label, non-randomised study to evaluate tolerance and acceptability of glibenclamide oral suspension in 10 patients with neonatal diabetes (age 0.3 to 16.2 years) including pharmacokinetic data (Neogli study, ClinicalTrials.gov Identifier: NCT02375828).

- Long-term follow-up safety study (Geneodia) with oral glibenclamide tablets (crushed or not) which includes children with neonatal diabetes treated in France since 2005 (Abstract).

The application for Amglidia 0.6 mg/ml and 6 mg/ml, oral suspension is an Article 10(3) hybrid application. In the hybrid dossier, reference is also made to nonclinical and clinical documentation included in the dossier of the reference medicinal product (Daonil® tablets).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral suspension containing either 0.6 mg/ml or 6 mg/ml of glibenclamide as active substance.

Other ingredients are hydroxyethylcellulose, lactic acid, purified water, sodium benzoate (E211), sodium citrate, and xanthan gum.

The product is available in a brown glass bottle (type III) with a child-resistant closure (polypropylene screw cap with polyethylene capsule inside). In addition, each bottle comes with 1 mL or 5 ml graduated oral syringe of LDPE and polypropylene depending on the presentation prescribed and an adaptor (LDPE) to be plugged on the bottle after opening for the syringe as described in section 6.5 of the SmPC.

General information

The chemical name of glibenclamide is 1-[[4-[2-[(5-chloro-2-methoxybenzoyl)amino]ethyl]phenyl] sulfonyl]-3-cyclohexylurea corresponding to the molecular formula $C_{23}H_{28}ClN_{23}O_5S$. It has a relative molecular mass of 494.00 g/mol and the following structure:

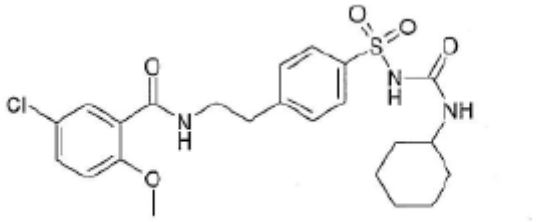

Figure 1 Glibenclamide structure

As there is a monograph of glibenclamide in the European Pharmacopoeia (Ph. Eur.), the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for glibenclamide, which has been provided within the current Marketing Authorisation Application.

Information on the elucidation of the chemical structure of the active substance is included in the CEP.

The active substance is a non-hygroscopic white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol (96 per cent) and in methanol. Glibenclamide is achiral.

Polymorphism has been observed for glibenclamide. Two polymorphs and two solvates of glibenclamide have been isolated and characterized. The solvates showed higher water solubility than polymorphs I and II. Form I was the most stable and was selected as the commercial form. A third polymorph (form III, recrystallization from a mixture of chloroform and ether) and another solvate (recrystallization from a mixture of carbon tetrachloride and chloroform) are described in the literature. Form III showed a higher solubility than form I and II and a lower melting point than form I. The authors concluded that form II and form III are metastable and that form I as the marketed form of the active substance is the stable form. A loss on drying test is systematically performed at release with the specification NMT 1.0% as described in the glibenclamide Ph. Eur. monograph to prevent formation of solvated forms. Glibenclamide is not hygroscopic and thus it is not likely to absorb water during storage. Based on these results, the active substance is present under the anhydrous polymorphic form I.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Glibenclamide is packed in polyethylene bags placed in an airtight HDPE drum.

Specification

The active substance is controlled according to the specification described in Table 1. These specifications are based on the Ph. Eur. monograph for glibenclamide.

The active substance specification includes tests for appearance (visual), solubility (Ph. Eur.), identification (melting point, UV and visible absorption, IR, TLC, and colour test), related substances (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (titrimetry), residual solvent (GC), particle size (laser granulometry), and polymorph identity (XRPD).

The control tests are carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents and particle size. Both additional methods have been adequately validated and described according to ICH Q2.

Batch analysis results are provided for 3 (1 pilot and 2 commercial) scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The relevant information was assessed by the EDQM before issuing the Certificate of Suitability. The retest period of the substance is 2 years when stored in double polyethylene bags placed in an airtight HDPE drum.

2.2.2. Finished medicinal product

Description of the product and Pharmaceutical development

The qualitative formulation of the oral suspension is presented in two concentrations, 0.6 mg/ml and 6 mg/ml in section 6.1 of the SmPC.

The active substance is practically insoluble in water and only slightly soluble in methanol. Therefore, the particle size is crucial for the performance of the finished product and its bioavailability. The active substance is micronized by the active substance manufacturer.

Polymorph identity is routinely tested by the active substance manufacturer to confirm that the polymorphic form of the micronized active substance is form I. It is systematically re-tested upon receipt by the finished product manufacturer by XRPD in order to ensure that transportation has not impacted the polymorphic form.

All excipients are conventional and widely used in oral solutions, and are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

A compatibility study between the active substance and the excipients likely to be used in the formulation was performed. Binary mixtures containing the active substance and each excipient inthe ratio of the most diluted final formula (0.6 mg/ml) were stored for 1 month at 40 °C/75% RH. After analysis by HPLC using the validated related substance analytical method, the results presented showed no impurity above the reporting threshold (0.10%).

The matrix formula of the suspension was established during development work. This formula can be used at a large range of pHs without affecting its consistency, in combination with different preservatives whose anti-microbial activity is directly dependent on the pH. Thus, the development strategy of the finished product was to introduce the active substance into this matrix formula and to subsequently define the preservative system and the target pH of the final product. Then, optimization steps were launched to verify the

homogeneity of the product, its stability under different conditions, and to improve the manufacturing process.

In order to evaluate the behaviour of the active substance in suspension, one “standard” formulation was prepared containing common compendial excipients used for this kind of pharmaceutical form. Two different preservatives have been tested: sodium benzoate and sodium methyl *para*-hydroxybenzoate (paraben). To characterize the final formulation and the adequacy with the objective of the development, different tests have been performed: visual appearance and sedimentation visual observation, microscopic examination, osmolality, and taste.

In order to test the effectiveness of the sodium benzoate preservative, batches containing 0, 0.25% and 0.5% were manufactured and evaluated in line with Ph. Eur. 5.1.3. The batch with no preservative was found to be contaminated whereas the preservative was found to be effective at the other 2 levels. Nonetheless, given the target population’s susceptibility to infection and the multi-dose container which will be opened on a daily basis, the higher level of preservative was selected to ensure effectiveness throughout the shelf-life. Instructions have been included in the SmPC with instructions as to which strength formulation should be used for which dose. This ensures that the amount of sodium benzoate never exceeds the acceptable daily intake (ADI) of 5 mg/kg/day. This approach was deemed acceptable.

CHMP also requested that the applicant manufacture batches containing only 90% of the nominal sodium benzoate to represent the worst case scenario which would still pass the release specification for sodium benzoate assay (90-110%) to investigate preservative efficacy over the proposed shelf-life. Two pilot scale batches were duly manufactured and stability studies instigated under long term and accelerated conditions. The studies were on-going at the time of CHMP opinion with only results from t_0 available. Therefore, the CHMP recommended that if an out of specification result is obtained at any time-point during these studies, a variation should immediately be submitted in order to amend the shelf-life and specification to ensure the on-going quality of the product throughout its shelf-life.

The stability of the formulations containing the different preservatives was investigated over 15 days at 50 °C. The content of both preservatives and the active substance did not change during the 15 days. A freeze thaw study (three 3-4 day cycles at -18 °C and 3-4 days at 40 °C/75% RH) were performed. After the different cycles, there was no significant change in the size or shape of the active substance crystals. Sodium benzoate was selected as the preservative as paraben is contra-indicated in neoneates and young children. The formulation used during clinical studies is the same as that intended for marketing.

Due to the very low solubility of glibenclamide, no dissolution method was initially developed. However, a dissolution method has finally been developed and validated using two batches. The results showed that the method was able to discriminate batches with different viscosity. However, the CHMP recommended that the applicant should review the dissolution data as new batches are manufactured (including the third validation batch) and tighten the specification limits by post-approval variation if appropriate.

The primary packaging is a brown glass bottle (type III) with a child-resistant closure (polypropylene screw cap with polyethylene capsule inside).The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Each bottle is provided with the following devices: one 1 mL or 5 mL graduated oral syringe of LDPE and polypropylene depending on the presentation prescribed and an adaptor (LDPE) to be plugged on the bottle. The medical devices are CE marked. The devices have been tested with the finished product (technical

batches manufactured for analytical purpose) according to Ph. Eur. 2.9.27 “Uniformity of mass of delivered doses from multidose containers”. All the results are compliant with the Ph. Eur.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 6 main steps. The process is considered to be a non-standard manufacturing process.

As the manufacturing process is considered non-standard, a manufacturing process validation report has been provided. The report presents the results from 2 batches per strength of the finished product. The manufacturing process is the same for both dosages. The presented process validation data was considered acceptable. However, according to the guideline on “process validation for finished products - information and data to be provided in regulatory submissions,” data on a minimum of 3 production scale batches should be submitted. Therefore, the CHMP recommended that the third validation batch be manufactured within 1 year and the completed validation report be provided as soon as available.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, smell, density (Ph. Eur.), viscosity (Ph. Eur.), osmolality (Ph. Eur.), dissolution (Ph. Eur.), uniformity of mass of delivered dose (Ph. Eur.), uniformity of content (Ph. Eur.), identification of glibenclamide (HPLC, DAD/HPLC), glibenclamide content (HPLC), identification of sodium benzoate (HPLC), sodium benzoate content (HPLC), impurities (HPLC), and microbiological control (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. In relation to the solubility specification, validation has been performed on two batches. The CHMP recommended that dissolution limits should be reconsidered in the light of dissolution data of the third validation batch and of the stability data generated. If warranted, the dissolution specification should be tightened by submission of the appropriate variation.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results (except for dissolution data) are provided for 3 commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 4 commercial scale batches per strength of the finished product stored upside down for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested using the same analytical methods as at release. The analytical procedures used are stability indicating. No significant changes have been observed under long term and accelerated conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. This study showed that unknown impurities were growing mainly in the finished product after a sun test exposure of 11 hours. These results confirm that the product is sensitive to light.

An in-use stability study has been performed to demonstrate that both strengths are stable for 30 days under the conditions likely to be encountered during routine use of the finished product. Samples were tested for container content interaction, assay of glibenclamide, assay of related impurities of glibencalmide, and determination of microbial contamination. The amount of glibenclamide and the impurity level in the sample remains stable during the study. This study has demonstrated that both suspensions are stable for 30 days after the first opening.

Based on available stability data, the proposed shelf-life of 36 months, with the bottle kept in the outer carton in order to protect from light as stated in the SmPC (section 6.3) is acceptable. In addition, the product should be used within 30 days of first opening, keeping the bottle tightly closed between uses.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.3. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product which the applicant has committed to resolving post-approval.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.5. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation.

- Considering the current absence of particle size data during shelf-life, the applicant should keep the proposed acceptance criteria and reassess them at the end of the stability study (at the latest), tightening them if necessary. Until two years long-term data are available, the applicant should perform a full re-test on each active substance batch just before using it to manufacture the finished product in order to check that all the tests are compliant with the current proposed specification.

- The third validation batch should be manufactured in a reasonable time (within 1 year) and the completed validation report will be provided as soon as available.

- If an out of specification result is observed at any time-point during the stability studies with batches manufactured with 90% of sodium benzoate, the applicant should immediately submit a variation in order to amend the shelf-life and specification to ensure the on-going quality of the product throughout its shelf-life.

- The applicant should provide new dissolution data as new batches become available (including the third validation batch) and consider the current proposed dissolution limit in the light of the dissolution data to the third batch and of the stability data generated. If warranted, the dissolution specification should be tightened by submission of the appropriate variation.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical

aspects of the SmPC are in line with the SmPC of the reference product, where appropriate. The impurity profile has been discussed and was considered acceptable. Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

Primary pharmacodynamics

Sulfonylureas (e.g. glibenclamide) are used for the treatment of non-insulin-dependent (type 2) diabetes mellitus. The hypoglycaemic effect of sulfonylureas is due to a stimulation of insulin secretion from pancreatic β-cells via blockade of the ATP-sensitive K^+ (K_{ATP}) channel (Sturgess et al. 1985; Trube et al. 1986; Zünkler et al. 1988a; Panten et al. 1989; review in Panten et al. 1996). The K_{ATP} channel couples cellular metabolism to membrane excitability. The K_{ATP} channel has first been described in guinea pig and rabbit cardiac myocytes (Trube and Hescheler 1984; Noma 1983) and later in pancreatic ß-cells (Ashcroft et al. 1984; Cook and Hales 1984; Rorsman and Trube 1985) but also in other tissues such as specific regions of the brain, skeletal and smooth muscles. In the pancreatic ß-cell the K_{ATP} channel regulates insulin secretion stimulated by nutrients like glucose; its metabolism in the pancreatic ß-cell mitochondria leads to ATP formation at the expense of ADP; this increased cytosolic ATP-to-ADP ratio results in closure of the K_{ATP} channels and membrane depolarization, activation of voltage-dependent Ca^{2+} channels followed by increases in intracellular Ca^{2+}, which then triggers the exocytosis of insulin-containing granules (review in Ashcroft and Rorsman 1991). The K_{ATP} channels are octamers of four pore-forming subunits of the inward rectifier Kir6.0 subfamily that includes Kir6.1 and Kir6.2 (Inagaki et al. 1995) and four regulatory SUR subunits that include SUR1, SUR2A and SUR2B (Aguilar-Bryan et al. 1995). The SUR subunit contains the binding sites for sulfonylureas. The pancreatic ß-cell K_{ATP} channel is formed by Kir6.2/SUR1 subunits (Inagaki et al. 1995) and Kir6.2/SUR2A form the cardiac K_{ATP} channel (Inagaki et al. 1996). ATP inhibits the pancreatic ß-cell and cardiac myocyte K_{ATP} channel via binding to the Kir6.2 subunit; in pancreatic ß-cells the presence of SUR1 can enhance the blocking action of ATP (Tucker et al. 1997).

Gain-of-function mutations in the genes encoding either Kir6.2 (KCNJ11; Gloyn et al. 2004) or SUR1 (ABCC8; Proks et al. 2006; Babenko et al. 2006) induce neonatal diabetes mellitus (NDM) via hyperpolarization of the pancreatic ß-cell resulting in reduced insulin secretion. The mutations increase K_{ATP} channel activity either via reducing block of ATP at the Kir6.2 subunit or by enhancing Mg-nucleotide stimulation at the SUR1 subunit (Koster et al. 2005). Transgenic mouse models carrying ATP-insensitive mutant K_{ATP} channels leading to the development of NDM have also been generated (Koster et al. 2000; Remedi et al. 2009). Neonatal diabetes is defined by hyperglycaemia within the first 6 - 9 months of life which is either permanent requiring lifelong therapy and is associated with Kir6.2 mutations or transient for which relapses can occur in adolescence and which is associated with SUR1 mutations. 20 - 30 % of patients also have neurological symptoms such as mental or motor developmental delay, muscle hypotonia, hyperactivity and epilepsy (DEND syndrome: **d**evelopmental delay, **e**pilepsy and **n**eonatal **d**iabetes). There is a correlation between the open probability of K_{ATP} channels and disease severity: mutations inducing the highest open probability of K_{ATP} channels located in the cerebral nervous system lead to the most severe form of NDM with neurological symptoms (DEND syndrome; Clark et al. 2010); in the absence of epilepsy, the syndrome is called intermediate DEND syndrome. Since mutations in Kir6.2 lead to higher open probabilities of the K_{ATP} channel compared to those of SUR1, most patients with the DEND syndrome have mutations in Kir6.2. Since the discovery of activating

mutations in K_{ATP} channels as the major mechanism underlying neonatal diabetes mellitus, most patients have been switched from insulin to sulfonylurea treatment (Pearson et al. 2006; Babenko et al. 2006). Mutations in either Kir6.2 or SUR1 subunits leading to NDM impair sulfonylurea-induced block of K_{ATP} channels to varying extent. Therefore, patients with NDM require higher sulfonylurea doses compared to adult patients with type 2 diabetes mellitus (reviews in Ashcroft and Rorsman 2013; Proks 2013). Transfer from insulin to sulfonylurea treatment of NDM was found to be best predicted by the in-vitro response of the specific Kir6.2 mutation to sulfonylurea-induced K_{ATP} current block and by the duration of diabetes (Babiker et al. 2015). Hyperglycaemia has glucotoxic effects leading to pancreatic ß-cell dysfunction, reduced ß-cell mass and insulin deficiency; therefore, the ability to treat NDM patients with sulfonylureas is inversely correlated with the duration of the disease and NDM patients should be treated with sulfonylureas as early as possible after diagnosis. In a mouse model of K_{ATP} channel-dependent NDM, hyperglycaemia and subsequent loss of ß-cells can both be prevented by chronic sulfonylurea treatment which induces permanent remission of NDM (Remedi et al. 2011). Furthermore, in NDM patients treated with sulfonylureas, there is a reduction in the required dose of sulfonylureas with time (review in Nichols and Remedi 2012). On the other hand, chronic glibenclamide treatment has been demonstrated to induce loss of insulin secretory capacity.

Safety pharmacology

Concerning safety pharmacology, the cardiovascular safety and possible neurotoxic effects of sulfonylureas are under discussion.

The study carried out by the University Group Diabetes Program (UGDP) in the early 1970s suggested that the use of tolbutamide was associated with an increased risk of cardiovascular mortality in patients with diabetes mellitus and co-existing coronary heart disease (University Group Diabetes Program 1970), which might be explained by sulfonylurea-induced block of cardiac K_{ATP} channels. Block of cardiac myocyte K_{ATP} channels under ischaemic conditions might either result in antiarrhythmic effects by preventing re-entry arrhythmias, or might lead to deleterious effects by augmenting the ischaemic damage or by abolishing ischaemic preconditioning. However, glibenclamide is sensitive (~ 10x) for the pancreatic ß-cell SUR1 vs. the cardiac myocyte SUR2A subunit, and glibenclamide did not alter cardiovascular mortality in the UKPDS study (1998). Therefore, from both a pre-clinical and clinical point of view, glibenclamide seems to be devoid of cardiac effects mediated via block of cardiac myocyte K_{ATP} channels. Glibenclamide oral suspension is administered at relatively higher doses in ND patients compared to adults, which potentially could affect cardiac SUR2A. However, due to the extreme rarity of ischemic heart disease in newborns and children this is considered to be not relevant.

K_{ATP} channels consisting of Kir6.2 and SUR1 subunits are expressed in both pancreatic ß-cells and in the brain, and an activation of K_{ATP} channels has a neuroprotective role in cerebral ischaemia. In streptozotocin-induced diabetic mice subjected to cerebral artery occlusion, the administration of tolbutamide increased neuronal injury, and a meta-analysis indicated that patients with type 2 diabetes mellitus treated with sulfonylureas have an increased risk of stroke (Liu et al. 2016). On the other hand, in the brain SUR1 is a regulatory subunit for the pore-forming Trpm4 subunit of a non-selective cation channel (NC_{Ca-ATP}), which is expressed under conditions of central nervous system injury (ischaemia). Opening of NC_{Ca-ATP} channels during cerebral ischaemia is depolarizing and is involved in edema formation, and in animal models of stroke glibenclamide has demonstrated neuroprotective effects (reduction of cerebral edema, infarct volume and mortality; Simard et al. 2006; review in Simard et al. 2012). Therefore, sulfonylureas have both detrimental and beneficial affects under conditions of cerebral stroke. Since SUR1 in combination with Kir6.2 has higher sulfonylurea affinity compared to SUR1 in association with Trpm4 and sulfonylureas are trapped within the

ischaemic brain, it was concluded that sulfonylurea treatment might contribute to an increased risk for stroke in the diabetic population (commentary by Parkinson and Hatch 2016).

2.3.3. Pharmacokinetics

Following oral administration of glibenclamide, the extent of absorption is 75 % in rats and > 90 % in rabbits and dogs (Kellner et al. 1969). In humans after oral administration of 5 mg glibenclamide, a C_{max} value of 90 nM was obtained (Rupp et al. 1969). Glibenclamide is a substrate for human organic anion-transporting polypeptide OATP-B, which is responsible for its uptake on the luminal membrane of intestinal epithelial cells (Satoh et al. 2005).

Glibenclamide is a weak acid (pKa value of 6.3) and is highly lipophilic (partition coefficient between octanol and water for the un-dissociated form of 94; Panten et al. 1989). Taking an extent of plasma protein binding of > 99 % into account, the therapeutically effective free plasma concentration of glibenclamide is < 10 nM (Panten et al. 1989). In all species tested (rats, rabbits and dogs) uptake into the brain was low (Kellner et al. 1969; Kaiser and Forist 1975). After s.c. administration, glibenclamide was not detectable in the brain of rats and after intracranioventricular administration of glibenclamide, glibenclamide was rapidly removed from the brain; the authors raise doubt whether the glibenclamide concentrations in the brain of DEND patients treated with p.os glibenclamide is high enough to inhibit neuronal K_{ATP} channel activity (Lahmann et al. 2015).

Glibenclamide crosses the placenta of pregnant rats (Sivan et al. 1995) and mice (Shuster et al. 2014), but transport via breast cancer resistance protein (BCRP) from the fetus to the mother limits the fetal distribution of glibenclamide in the pregnant mouse (Zhou et al. 2008) and in the perfused rat placenta (Cygalova et al. 2009). In humans glibenclamide is also actively transported via BCRP from the fetus to the mother and is not detectable in the human fetus (Kraemer et al. 2006; Pollex et al. 2008). In breast-feeding women given oral doses of 5 - 10 mg glibenclamide, no glibenclamide was detected in breast milk (Feig et al. 2005). Glibenclamide inhibits p-Glycoprotein and is a substrate for this transporter (Golstein et al. 1999).

The main metabolites in humans are the 4-trans (M1) and 3-cis (M2) hydroxyl derivatives (Rupp et al. 1969); both are also found in the rabbit, whereas only metabolite M2 is found in rats and dogs. Therefore, regarding drug metabolism, the rabbit most closely resembles humans. Both metabolites have pharmacological effects which are lower compared to the parent substance (Rydberg et al. 1994).

In the human liver, glibenclamide is metabolized mainly by cytochrome P450 iso-enzyme CYP3A4, and to a minor extent by CYP2C19, CYP2C9 and CYP2C8 (Naritomi et al. 2004; van Giersbergen et al. 2002; Zharikova et al. 2009; Zhou et al. 2010). The CYP iso-enzymes in neonates and children are sufficiently developed in order to metabolize glibenclamide in a similar manner as in adults.

Elimination half-lives are 1.4 - 2.8 h in rats, 7.4 - 8.6 h in rabbits, 3.7 - 4.3 h in dogs and about 4.8 h in humans; values for clearance are 0.15 - 0.25 ng/ml in rats, 0.56 - 0.74 ng/ml in rabbits and 0.28 - 0.52 ng/ml in dogs. Dogs and rats excrete 90 % of the dose in faeces via biliary secretion, whereas both in rabbits and in humans 50 % of the dose is excreted in both faeces and urine, respectively (Kellner et al. 1969; Kaiser and Forist 1975; Rupp et al. 1969).

2.3.4. Toxicology

The acute toxicity of glibenclamide is low after oral administration (LD50 values > 10 g/kg in mice, rats, rabbits, guinea-pigs and dogs). In repeated dose toxicity studies with oral administration of glibenclamide, effects on pancreatic ß-cells were observed (enlargement of the islets of Langerhans with irregularly configured islets and reduction in pancreatic β-cell granulation in rats, ß-cell exhaustion as indicated by depletion of insulin-containing granules in rabbits; Hebold et al. 1969; Mizukami et al. 1969 and Webster et al. 1975).

Available data of in vitro and in vivo studies do not show any evidence for genotoxicity of glibenclamide.

After oral administration for 18 months in rats and for 2 years in mice, no carcinogenic effects of glibenclamide were observed.

Glibenclamide did not affect male and female fertility in rats and mice. When orally administered during organogenesis glibenclamide did not induce any teratogenicity in rats, mice and rabbits, respectively. Glibenclamide administration throughout gestation and lactation did not affect litter size, birth weights and viability of the F1-generation in rats and mice.

No juvenile toxicity study was conducted. This is in line with the Paediatric Investigational Plan (PIP) submitted for this product, in which it was argued that nonclinical safety could be assessed on the basis of the existing published data, without the need for further studies. A positive opinion was given by the Paediatric Committee on 19 July 2013, with final CHMP Decision (Decision N° P/0209/2013) on 3 September 2013. Concerns raised during the CHMP assessment of the marketing authorisation application, such as age dependent maturation of the metabolic systems relevant for glibenclamide and the development of the blood-brain barrier were adequately addressed by the applicant. Since clinical data in the paediatric population are already available, no non-clinical studies were requested by the CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

An updated ERA was submitted.

Table 1 Summary of main study results

Substance (INN / Invented Name): Glibenclamide			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.23	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000032	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

An adequate ERA in accordance with available guidance was performed. The predicted environmental concentration in surface water of glibenclamide is below 0.01 µg/l. The log Kow is lower than 4.5, no further PBT assessment is required. In conclusion, Amglidia, in the proposed use, is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Several pharmacology studies published in high-impact journals clearly demonstrate the effect of glibenclamide in NDM caused by activating mutations in pancreatic ß-cell K_{ATP} channels. A clear correlation between the in-vitro sensitivity of mutated pancreatic ß-cell K_{ATP} channels towards sulfonylurea-induced block and the effectiveness of sulfonylureas for the treatment of NDM was found. The Applicant has provided a comprehensive list of mutations in genes encoding for Kir6.2 and SUR1 leading to NDM, the in-vitro sensitivity of these mutations towards sulfonylurea-induced K_{ATP} current block, and the responses of patients carrying these mutations to sulfonylurea treatment. Functional *in-vitro* data are not necessary for determining the therapeutic dose in clinical practice because this can be done by titration of glibenclamide according to blood glucose level. However, these data provide a strong rationale that treating patients carrying KCNJ11 or ABCC8 mutations with glibenclamide is a suitable approach.

Concerning the pharmacokinetics of glibenclamide, the blood-brain-permeability of glibenclamide is under scientific discussion, although some published data suggest effectiveness of glibenclamide in NDM patients with neurological symptoms (iDEND and DEND syndromes).

The toxicology studies of glibenclamide were performed several decades ago, but due to the wide clinical experience with glibenclamide no further studies are required.

2.3.7. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Amglidia was provided and was accepted by the CHMP. Additional non-clinical studies were not considered necessary by the CHMP.

The discovery that gain-of-function mutations in the genes encoding the subunits of the pancreatic ß-cell K_{ATP} channel cause NDM and that the affected children can be switched from insulin to sulfonylurea therapy is a milestone in the field of diabetes mellitus.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for an oral suspension containing glibenclamide. To support the marketing authorisation application the applicant conducted one bioavailability study with cross-over design under fasting conditions. This study was the pivotal study.

Furthermore, a tolerance and acceptability study was conducted, and bibliographical data were submitted.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Academic publications contribute an important amount of data on which this hybrid application is based. This is most prominent for the data published by Babenko et al. (NEJM, 2006), Pearson et al. (NEJM, 2006) and Beltrand et al. (Diabetes Care, 2015). No information is available in respect to GCP or GLP compliance in the studies underlying the publications. However, this is considered acceptable in this application.

Clinical studies

An overview of the main clinical studies is presented in table 5.

Table 2 Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioavailability	1AMK1 /Glibentek1	5.3.1.2	Compare the relative bioavailability of two new oral glibenclamide suspensions (Formulation A= 0.83 mL of a 30mg/5mL suspension and Formulation B = 8.33 mL of the 3mg/5mL suspension) and of 5mg of Daonil® crushed tablet (Reference Formulation C), after single oral administration, in fasted conditions	Phase I, single-center, open-label, randomised, single-dose, three-period, six-sequence, crossover study	Glibenclamide 0.6 mg/ml and 6 mg/ml oral suspension DAONIL® Glibenclamide 5 mg tablet Oral	18	Healthy male volunteers	Single dose	Pharmaco-kinetics Final Report 10 February 2012
Tolerance and Acceptability	Neogli P130904	5.3.5.4	Assess the acceptability of an oral glibenclamide suspension, in patients with very early onset diabetes due to a mutation in Kir6.2 or SUR1	Phase II single-centre, non-randomised, open-label, prospective study	Glibenclamide 0.6 mg/ml and 6 mg/ml oral suspension Oral suspension of crushed DAONIL® Glibenclamide 5 mg tablet Oral	10	Children affected by neonatal or very early onset diabetes due to a mutation of the KCNJ11 or ABCC8 gene coding for the 2 types of Kir6.2 or SUR1 sub-unit of ATP-dependent potassium channels on pancreatic beta cells	1 to 3 months	Other clinical study. Final Report October 2016

2.4.2. Pharmacokinetics

Study No: 1AMK1/Glibentek1

Title of Study:
Study of the relative bioavailability of two glibenclamide suspensions versus crushed tablets of the reference product, Daonil® 5 mg

Study design:
A phase I, single-center, open-label, randomised, single-dose, three-period, six-sequence, crossover study in 18 healthy male subjects.

Study Center(s):

Clinical and Statistical Evaluation

Biotrial PARIS, 1 rue Charles Drot, BP 18, 92502 Rueil-Malmaison, FRANCE

Analytical Laboratory

Anapharm Inc., 2050 boul. Rene-Levesque Ouest, Sainte-Foy, Qc, Canada

Study Periods:
Clinical Phase: 31 May 2011 to 25 July 2011
Analytical Phase: 11 Aug 2011 to 23 Aug 2011

Test and Reference Products:

Name of Test Drug / Investigational Product:
Treatment A
Glibenclamide 30 mg/5 mL (6 mg/ml) oral suspension
UNITHER Developpement Bordeaux
Batch no.: CLI6629 (CPM7681)
Expiry Date: 19 Oct 2012

Treatment B
Glibenclamide 3 mg/5 mL (0.6 mg/ml) oral suspension
UNITHER Developpement Bordeaux
Batch no.: CLI6629 (CPM7680)
Expiry Date: 11 Oct 2012

Name of Reference Drug:
Treatment C
DAONIL® 5 mg tablets
Sanofi, France
Batch no.: CLI6629 (9KP4A)
Expiry Date: 29 Feb 2012

Pharmacokinetics results

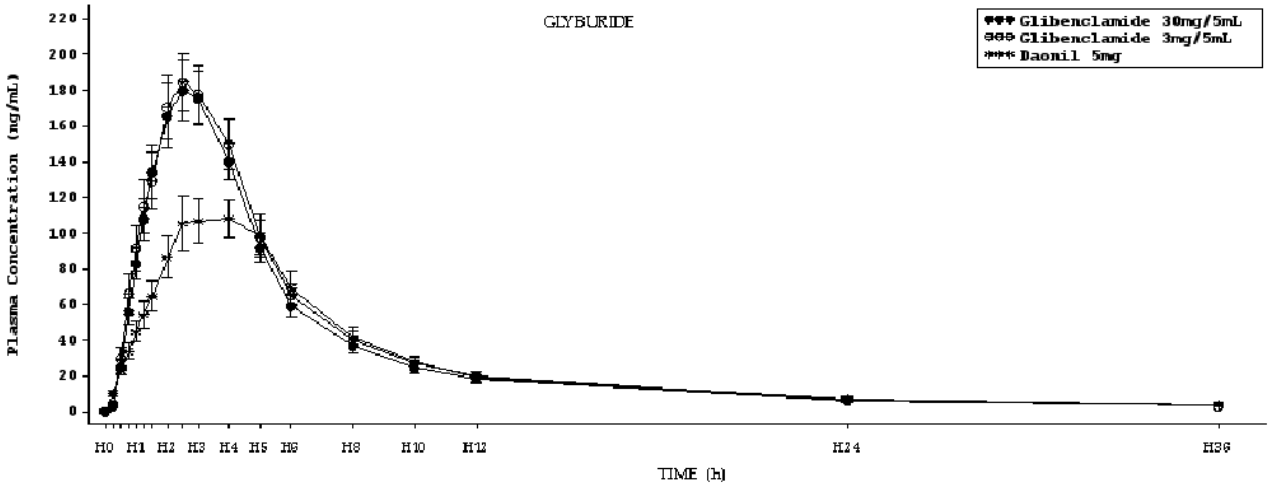

Figure 2 Mean plasma profiles of 3 oral formulations (single dose) of glibenclamide 5 mg over time - (Pharmacokinetic set, N=18) - Linear scale

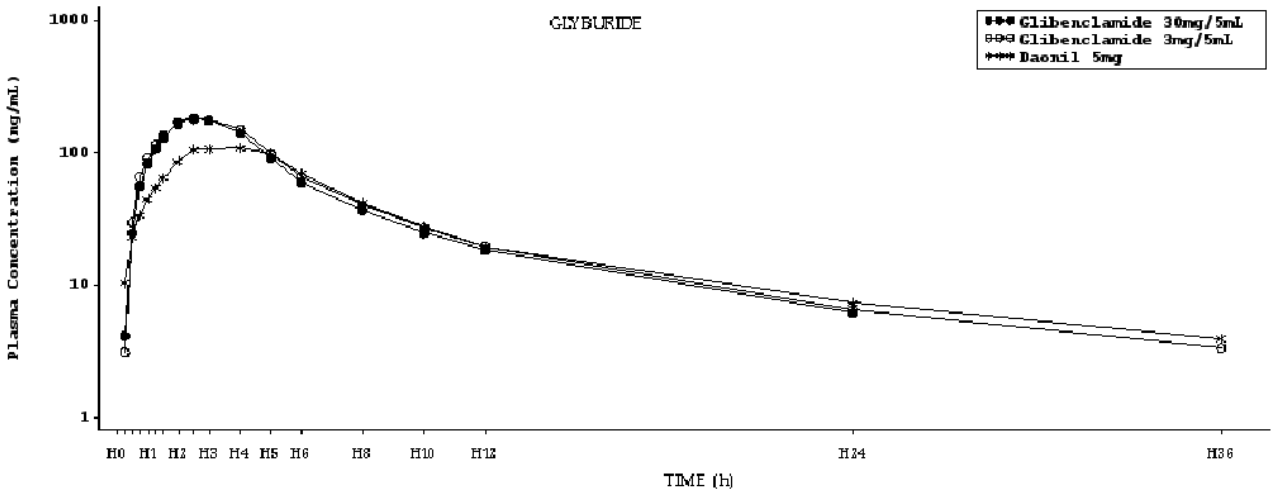

Figure 3 Mean plasma profiles of 3 oral formulations (single dose) of glibenclamide 5 mg over time - (Pharmacokinetic set, N=18) - Log-linear scale

Table 3 Glibenclamide 5 mg pharmacokinetics (Pharmacokinetic set, N=18)

Treatment		C_{max} (ng/mL)	t_{max}* (h)	λz (h-1)	$T_{1/2}$ (h)	$AUC_{0-tlast}$ (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)
	N	18	18	18	18	18	18
Glibenclamide	Arithmetic Mean	201.71	2.50	0.0944	8.22	1060.5	1120.9
30 mg/5 ml	SD	71.43	(1.50-4.00)	0.0246	4.04	399.2	400.5
	CV%	35.4		26.1	49.2	37.6	35.7
	N	18	18	18	18	18	18
Glibenclamide	Arithmetic Mean	206.93	2.50	0.1004	7.76	1133.3	1172.3
3 mg/5 ml	SD	67.33	(2.00-4.00)	0.0355	2.67	422.1	422.0
	CV%	32.5		35.3	34.4	37.2	36.0
	N	18	18	18	18	18	18
Daonil	Arithmetic Mean	148.34	3.00	0.0773	10.45	923.0	995.6
5 mg	SD	46.74	(1.25-5.00)	0.0288	4.45	314.6	321.1
	CV%	31.5		37.3	42.6	34.1	32.3

*: For t_{max} (Median (min-max))

Conclusion of Bioavailability Study (1AMK1/Glibentek1)

When glibenclamide suspensions were administered in 18 healthy male subjects, glibenclamide plasma concentrations peaked 0.5 hour earlier than those observed with a crushed Daonil tablet (median value of 2.5 hours post-dose versus 3.00 hours post-dose). Mean plasma peak Cmax values were similar for the two suspensions, with values of 201.71±71.43 ng/mL for the 30 mg/5mL suspension and 206.93±67.33 ng/mL for the 3 mg/5 ml suspension. These values were approximately 40% higher than those obtained for the crushed tablet (148.34±46.74 ng/mL).

Exposures were similar for the two suspension dosages (AUC0-∞ values of 1120.9 ±400.5 ng.h/mL and 1172.3±422.0 ng.h/mL for the 30 mg/5 mL and 3 mg/5 mL suspensions, respectively), and higher than the exposure observed after Daonil administration. Relative bioavailability was 121.6% for the 3 mg/5 mL

formulation and 114.1% for the 30 mg/5 mL formulation (see Appendix 14.4.2.2.) when compared to the Daonil crushed tablets.

Elimination half-lives were similar for the two suspensions (close to 8 hours) and a little shorter than those observed with Daonil crushed tablets (10.45 hours).

Study No: NEOGLI – P130904

Title of Study:
Tolerance and acceptability of Glibenclamide suspension in patients with diabetes secondary to mutation of the ATP-sensitive potassium channels (Kir6.2 or SUR1)

Study design:
A phase II, single-centre, prospective, open-label, non-randomised study

Study Periods:
The first patient of the NEOGLI study was enrolled on 20 March 2015 and, due to the rarity of the disease and the very slow recruitment, the treatment of the last 10th children was completed end March 2016.

Study Center(s):
The Paediatric Endocrinology, Gynaecology and Diabetology Department, Necker University Hospital, Paris (France)

Test and Reference Products:

Name of Test Drug/Investigational Product:
Glibenclamide 3 mg/5 mL (0.6 mg/ml) oral suspension

UNITHER Developpement Bordeaux

Batch no.: CPM-8451-000

Expiration date: 12/2017

Glibenclamide 30 mg/5 mL (6 mg/ml) oral suspension

UNITHER Developpement Bordeaux

Batch no.: CPM-8452-000

Expiration date: 01/2018

Name of Reference Drug:
DAONIL® 5 mg tablets used off-label

Sanofi, France

Batch no.: Not applicable

Treatment

At inclusion (Day 0, D0), patients were all treated with the classical form of glibenclamide (tablet or crushed tablet). Two to 4 blood samples for the determination of glibenclamide concentration were drawn for each patient at pre-dose (T0) and sparsely during the first four hours after drug administration.

After 1 month, the switch was made to the glibenclamide oral suspension formulation and at month 2 (M2), another pharmacokinetic sampling was conducted.

Pharmacokinetic Results

A total of 10 patients with 42 concentration time points were available for analysis:

- 24 concentrations for the solid formulation (glibenclamide tablets)

- 18 concentrations for the liquid formulation (glibenclamide oral suspension)

From the 10 patients available, 7 had concentrations before and after the switch (i.e., for both formulations).

Table 4 Number of pharmacokinetic samples per patient

Patient ID	Tablets[a]	Oral suspension[b]
001-0001	3	3
001-0002	2	2
001-0003	4	4
001-0004	3	3
001-0005	2	2
001-0006	1	2
001-0007	3	0
001-0008	2	0
001-0009	2	0
001-0010	2	2
Total	**24**	**18**

Table 5 Individual Glibenclamide PK parameters after administration of tablets or oral suspension

Patient ID	Daily Dose (mg)		Clearance/F (l/h/kg)*		Volume/F (l/kg)*		AUC(µg×h/l)		Tmax, h		F_{rel}
	tablets	oral suspension	tablets	oral suspension	tablets	oral suspension	tablets	oral suspension	tablets	oral suspension	
001-0001	4.5	3.54	0.22	0.28	2.23	2.84	881.63	851.36	3.27	3.29	0.78
001-0002	5.5	0.66	0.21	0.06	1.47	0.43	3732.86	109.23	2.89	2.95	3.46
001-0003	3.12	2.4	0.08	0.13	0.77	1.18	1281.52	1489.77	3.19	3.19	0.65
001-0004	1.86	1.44	0.1	0.08	0.91	0.68	766.98	438.04	3.15	3.16	1.34
001-0005	7	3.3	0.37	0.12	3.39	1.17	1505.86	223.63	3.16	3.2	2.88
001-0006	1.9	1.02	0.26	0.13	2.18	1.07	684.59	181.17	3.05	3.05	2.03
001-0007	22.5	0	0.21	-	2.53	-	2296.5	-	3.5	-	-
001-0008	1.2	0	0.36	-	3.12	-	300.77	-	3.12	-	-
001-0009	5	0	0.28	-	2.6	-	1169.29	-	3.18	-	-
001-0010	2.1	1.8	0.13	0.12	0.88	0.84	2288.88	1689.69	2.81	2.85	1.04
mean±SD	5.5±6.3	1.4±1.3	0.22±0.1	0.13±0.09	2±1	1.2±0.9	1490.9±1023.1	711.8±632.7	3.1±0.2	3.1±1.5	1.7±1.2
median	3.81	1.23	0.215	0.12	2.205	1.07	1225.405	438.04	3.155	3.16	1.34
IQR	1.95-5.38	0.17-2.25	0.15-0.28	0.1-0.13	1.05-2.58	0.76-1.18	795.64-2093.13	202.4-1170	3.07-3.19	3-3.2	0.91-2.46
min-max	1.2-22.5	0-3.5	0.1-0.4	0.06-0.28	0.77-3.39	0.4-2.8	300.8-3732.9	109.2-1689.7	2.8-3.5	2.9-3.3	0.7-3.5

** F = 1 for tablets; F = F_{rel} for oral suspension.*

F_{rel}, *bioavailability of oral suspension relative to tablets*

Conclusion of NEOGLI study

Individual pharmacokinetic parameters after administration of glibenclamide tablets or oral glibenclamide suspension were assessed in the NEOGLI study.

Due to the extreme rarity of the condition, the number of patients included in the NEOGLI study was very limited. From the 10 paediatric patients available, 7 had concentrations before and after the switch, i.e. for both formulations. Different daily doses were administered with a median dose of 3.81 mg/day (ranging from 1.2 to 22.5 mg/day) for the tablets and a median dose of 1.23 mg/day (ranging from 0 to 3.5 mg/day) for the glibenclamide oral suspension formulation.

When the child is on stable dose of glibenclamide tablets, the starting dose of glibenclamide suspension should be reduced, and given with the same numbers of intake per day as it was done in the pivotal NEOGLI study; a starting dose reduction for the suspension, as compared to glibenclamide tablets is required due to the higher bioavailability of the glibenclamide suspension. Subsequently dose adjustment as described in SmPC Section 4.2 Posology should be applied.

The presented PK results of the NEOGLI study are highly variable and rather descriptive due to the limited number of patients and different daily doses used. No further statistical and clinical meaningful conclusion can be drawn.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Mechanism of action

The ATP-sensitive potassium channel (or KATP channel) is a type of potassium channel that is gated by intracellular nucleotides, ATP and ADP. ATP-sensitive potassium channels are composed of Kir6.x-type subunits and sulfonylurea receptor (SUR) subunits. Of particular importance here are the KATP channels in pancreatic ß-cells (Kir6.2/SUR1). In vascular myocytes KATP is Kir6.1/SUR2B. The KATP in cardiac and skeletal myocytes is assumed to be predominantly Kir6.2/SUR2A while the dominating KATP in neuronal cells is Kir6.2/SUR1 (= ß-cell-type).

Sulfonylureas such as glibenclamide work by binding to and inhibiting the ATP-sensitive potassium channels (KATP) in pancreatic ß-cells. This inhibition causes cell membrane depolarization, provoking opening of voltage-dependent calcium channels. This results in an increase in intracellular calcium in the ß-cell and subsequent stimulation of insulin release.

Glibenclamide has an approximately 10-20 times higher binding affinity to the pancreatic than to the cardiovascular KATP-channels (Quast et al. 2004).

A model of action of sulphonylurea on β-cells expressing mutations in the Kir6.2 subunit of the KATP channel has been proposed by Pearson (Pearson et al, 2006) and is presented below. The mechanism is applicable on mutations of the SUR1 subunit as well.

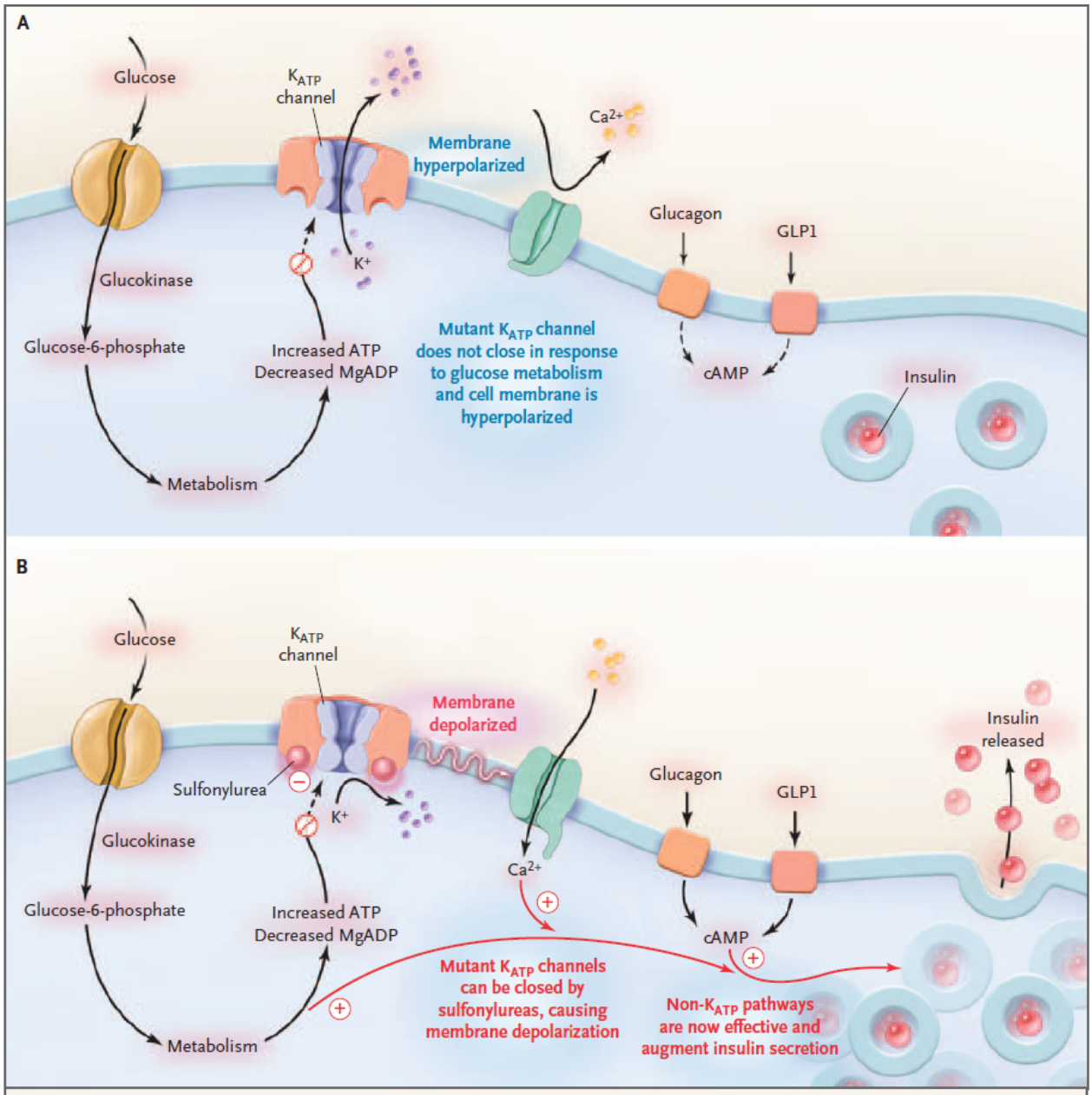

Figure 4. Proposed Model of the Action of Sulfonylurea on Beta Cells Expressing Mutations in the Kir6.2 Subunit of the K_{ATP} Channel.

In Panel A, glucose enters the beta cell and is metabolized, which leads to an increase in intracellular ATP and a decrease in magnesium ADP (MgADP).[23-25] Since mutations in the Kir6.2 subunit of the K_{ATP} channel are less sensitive to ATP inhibition, K_{ATP} channels remain open in the presence of glucose, which keeps the plasma membrane hyperpolarized. This hyperpolarization keeps voltage-gated calcium channels closed, preventing calcium influx and insulin release. Other stimuli, such as GLP1, are ineffective because the membrane is hyperpolarized and cytosolic calcium levels remain low. In Panel B, sulfonylureas bind to the SUR1 subunit of the K_{ATP} channel, closing mutant K_{ATP} channels, which results in membrane depolarization. This process triggers the opening of voltage-gated calcium channels, causing calcium influx and a small increase in insulin release. The rise in the level of intracellular calcium renders potentiators of insulin secretion, such as incretins (e.g., GLP1), capable of augmenting insulin secretion. It is also possible that the sulfonylurea dose may not be sufficient to depolarize the membrane completely but that GLP1, for example, can produce an additional small depolarization that facilitates calcium influx if most K_{ATP} channels are shut.[26]

Figure 4

Discussion on clinical pharmacology

The 1AMK1/GlibenTek1 study was performed to compare the relative bioavailability of single oral administration in fasted conditions of oral suspensions of glibenclamide (0.6 mg/ml and 6 mg/ml) with oral crushed Daonil® tablets (non-micronized) in healthy male adult volunteers. This study allowed to determine the starting dose when a child is transferred from off label use crushed Daonil® non-micronized tablets to the glibenclamide oral suspension; when the child is on a stable dose of crushed glibenclamide tablets (non-micronized), the starting dose of glibenclamide suspension should be decreased by 18% for the 0.6 mg/ml formulation and by 12 % for the 6 mg/ml, respectively, with the same numbers of intake per day.

The presented PK results of the NEOGLI study are highly variable and rather descriptive due to the limited number of patients and different daily doses used. No further statistical and clinically meaningful conclusions can be drawn from the NEOGLI study.

The pharmacodynamics and especially the mechanism of action of sulfonylureas such as glibenclamide is well understood, providing a sound rationale for the treatment of children with NDM due to mutations in the β-cell ATP-sensitive potassium channel with Amglidia.

Conclusions on clinical pharmacology

The clinical pharmacology and PK/PD approach of this Article 10.3 hybrid application is considered acceptable in view of the extreme rare disease of neonatal diabetes.

A higher bioavailability was found for the oral suspension compared to glibenclamide crushed tablets (non-micronized). The dosing recommendations (“the starting dose of glibenclamide suspension should be decreased by 18% for the 0.6 mg/mL formulation and by 12 % for the 6 mg/mL, respectively, with the same numbers of intake per day.”) given in the proposed SmPC adequately reflect this finding. However, micronized and non-micronized glibenclamide tablets are available in the EU member states with the micronized formulation providing seemingly better absorption of glibenclamide. Therefore, the starting dose identified for switching patients from non-micronized glibenclamide to Amglidia cannot easily be transferred to the non-micronised formulation. For the latter, no switching data are available and thus the conversion rate between micronized tablets and the suspension has not been established. This issue is appropriately reflected in the product information.

2.4.4. Clinical efficacy

The efficacy of glibenclamide oral suspension in the treatment of ND is supported by bibliographical data and an efficacy, tolerability and acceptability study in 10 patients with ND (NEOGLI).

Neonatal diabetes mellitus (NDM) is a rare genetic disorder occurring in around 1/90000 to 1/260 000 live births characterised by diabetes that presents within the first 6 months of life and which may be either permanent (PNDM) or transient (TNDM). Considerable overlap occurs between the two groups, so that TNDM cannot be distinguished from PNDM based on clinical features. Newborns with NDM associated with a defect of β-cell function present hyperglycaemia, failure to thrive, as well as dehydration, ketoacidosis, and coma, and they require exogenous insulin therapy to obtain metabolic control and avoid death.

Approximately 50% of cases of neonatal diabetes are due to gain-of-function mutations in the genes that encode the pore-forming (KCNJ11) or regulatory (ABCC8) subunits of the β-cell ATP-sensitive potassium

(K_{ATP}) channel. In ~30% of these patients, neurological symptoms such as developmental delay and muscle hypotonia are also found, a condition termed intermediate DEND (iDEND) syndrome. About 3% of patients also experience epilepsy (DEND syndrome, defined as **d**evelopmental delay, **e**pilepsy and **n**eonatal **d**iabetes).

More than 50 Kir6.2 variations and more than 70 SUR1 variations associated with NDM have been reported. The variants V59M, R201C and R201H of Kir6.2 are the most frequently observed mutations of K_{ATP}-channels leading to NDM. Though there is a correlation between the certain amino acid exchange and severity of the syndrome (TNDM, PNDM, iDEND and DEND) no one to one association is observed.

Dose-response studies and main clinical studies

No dose response studies were conducted. In adult patients with type 2 diabetes mellitus the daily dose of glibenclamide is up to 15 mg.

In the initial studies with paediatric patients with NDM a titration protocol was used:
The glibenclamide dose is increased daily by 0.2 mg per kg per day in two divided doses. As the dose is increased it is usually possible to reduce and then stop the insulin dose. This reduction in insulin is achieved after the first day by the use of only short acting insulin enabling rapid titration of insulin dose depending on the pre-meal glucose. The finding of pre-meal capillary glucose values are < 7 mmol per litre either pre-breakfast and or before the evening meal is taken as an indication to reduce the insulin dose (usually by 50% of the normal pre-meal insulin dose) and keep the glibenclamide dose unchanged. However, if subsequent pre-meal capillary blood glucose values are >7 mmol per litre then glibenclamide dose titration could be recommenced.

In Pearson, 2006 a graph with the sulfonylurea doses for 12 patients who had switched from insulin to sulfonylurea therapy is shown.

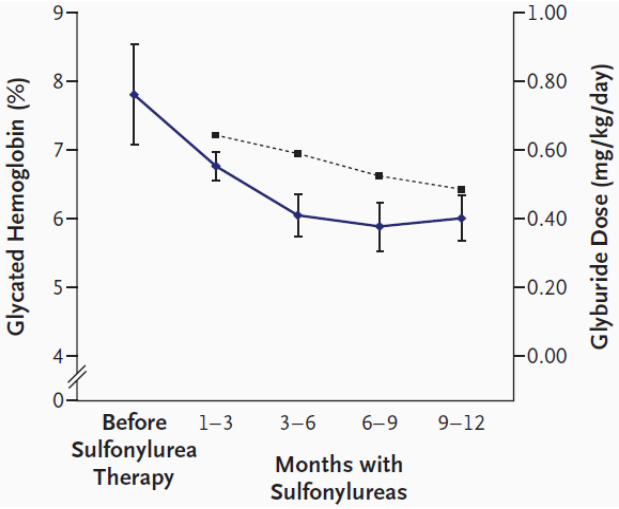

Figure 5

The doses required are high when calculated on a per kg body weight basis compared with adults with type 2 diabetes, typically needing around 0.5mg/kg/d of glibenclamide, although doses as high as 2.3 mg/kg/d have been occasionally reported . When compared with Kir6.2 patients, SUR1 patients needed lower doses of sulfonylureas after transfer (0.26 vs. 0.45 mg/kg/day).

A titration and dosing regimen based on these experiences has been proposed by the applicant. The proposed starting dose of 0.2 mg/ kg/ day has been used in the published studies and is considered to be effective. As appropriate during treatment with any hypoglycaemic agent, the doses of glibenclamide will be adapted by titration in each individual patient.

Many patients have been able to progressively reduce the dose of sulfonylurea after transition while maintaining good glycaemic control.

Treatment induction includes analyses of C-peptide. An increase in C-peptide after start of sulfonylurea therapy might be a meaningful guide for estimating the response of the patient. However, this is still in the domain of research and cannot yet be a recommended parameter to be used in clinical practice.

Summary of main efficacy results

NDM, diagnosed within the first 3 months of life, is a rare condition occurring in around 1/90000 to 1/260 000 live births. The clinical features are specific and different from the usual diabetes mellitus in children (type 1 auto-immune diabetes mellitus). Neonatal diabetes (ND) is associated with a defect of β-cell function. The three major genetic anomalies linked to neonatal diabetes mellitus are chromosome 6 anomaly, K_{ATP}-channel mutations or insulin gene mutations. Transient neonatal diabetes resolves by a median of 12 weeks and is frequently associated with an abnormality of the chromosome region 6q24. In contrast, permanent neonatal diabetes requires (insulin) treatment for life.

The physiological importance of K_{ATP} channels in insulin secretion was established 30 years ago. At substimulatory glucose concentrations, K^+ efflux through open K_{ATP} channels maintains the β-cell membrane at a hyperpolarized potential of around -70 mV, which keeps voltage-gated Ca^{2+} channels closed. Elevation of the blood glucose concentration increases glucose uptake and metabolism by the β-cell, producing changes in cytosolic nucleotide concentrations that cause K_{ATP} channel closure. This leads to a membrane depolarization that opens voltage-gated Ca^{2+} channels initiating β-cell electrical activity and Ca^{2+} influx, and the subsequent rise in $[Ca^{2+}]_i$ triggers exocytosis of insulin granules.

Approximately 50% of cases of neonatal diabetes are due to gain-of-function mutations in the genes that encode the pore-forming (KCNJ11) or regulatory (ABCC8) subunits of the β-cell ATP-sensitive potassium (K_{ATP}) channel leading to dysfunctional K_{ATP} channel and.

Prior to the discovery that NDM can be caused by mutations in the K_{ATP} channel, many patients were assumed to be suffering from early-onset type 1 diabetes. Accordingly they were treated with insulin injections. Recognition that these patients actually possess gain of function mutations in K_{ATP} channel genes rapidly led to a switch to sulphonylurea treatment. To date, many patients with NDM caused by mutations in Kir6.2 or SUR1 have been successfully transferred to sulphonylureas. This results in improved glycaemic control without increasing the risk of hypoglycaemia or even fewer hypoglycaemic events and a simpler medication regime. Approximately 90% of patients with activating mutations in the K_{ATP} channel genes can be transferred from insulin onto sulfonylurea tablets.

Studies have established that ~20% to 30 % of patients with mutations in K_{ATP} genes have abnormalities of the standard neurological evaluation ranging from mild to severe developmental delay. The concomitant presence of treatment resistant epilepsy and muscle weakness is known as **d**evelopmental delay, **e**pilepsy and **n**eonatal **d**iabetes (DEND) syndrome; intermediate DEND is a less severe phenotype without epilepsy. However, appropriate testing methods detected developmental impairments in >70% of patients with K_{ATP} gene mutations. Several observations support a direct effect of the K_{ATP}-channel mutations on the central

nervous system. These impairments adversely affect academic performance, social functioning, and quality of life. Sulfonylurea (SU) therapy may improve such neurological impairments since K_{ATP} channels are found in many tissues, including the brain, and play a role in membrane polarization and cell functions. It has been reported that SU therapy in neonatal diabetes secondary to mutations in potassium-channel subunits produces measurable improvements in neuropsychomotor impairments, which are greater in younger patients (Beltrand et al. 2015). The observation that glibenclamide most probably does not enter the CNS, the selectivity of glibenclamide for SUR1 and the expression pattern of SUR1 being prominent only in the pancreatic ß-cells and the brain contradict this assumption. Therefore, the extent to which neurological features respond to glibenclamide is uncertain. A study in France with 18 patients suggests that SU therapy improves neurodevelopmental parameters in patients with neonatal diabetes owing to potassium-channel subunit mutations and acts via a central mechanism (GlidKir-study, Beltrand et al. 2015). However this study was uncontrolled due to ethical reasons. Similar observations were reported by others (Busiah et al. 2013, Proks 2013). The improvements have been greater in younger patients.

To date, available functional studies (Hattersley and Ashcroft 2005) show that increase in channel activity produced by mutations in SUR1 is smaller than that caused by Kir6.2 mutations. This may explain the relative high incidence of TNDM than PNDM among patients with ABCC8 mutations as well as why most patients with DEND syndrome (>90%) have mutations in Kir6.2. Knowledge of the specific mutation can help predict whether successful transfer to sulfonylureas is likely. In addition to the specific mutation shorter diabetes duration is associated with successful transfer to insulin independence. Genetic testing is considered mandatory in all cases of NDM; however, sulfonylurea treatment before such results are available may be considered due to the potential benefits.

About 50% of type 2 diabetic patients treated with glibenclamide experience a severe deterioration of metabolic control within 6 years of therapy initiation. Nevertheless, it should be noted that the pathophysiology observed in patients with type 2 diabetes is strikingly different from that in individuals with NDM due to K_{ATP}-channel mutations. Long-term data arguing for a persistent beneficial effect of SU in NDM are very limited. In 11 patients with KCNJ11-associated PNDM, retained HbA_{1c} control with SU for more than 57 month was reported (Iafusco et al. 2011). The sulfonylurea dose (mg kg^{-1} day^{-1}) was progressively reduced in all these cases. Additional preliminary data suggest that efficacy is maintained for at least 10 years (GENEODIA study, Hoarau et al. 2016).

In the agreed paediatric investigation plan (PIP), the Paediatric Committee (PDCO) requested that data on the pharmacokinetics of glibenclamide oral suspensions be collected in the “Acceptability and tolerance study” (**NEOGLI study**) in which children treated for NDM were switched from tablets or crushed glibenclamide tablets to the glibenclamide suspension.

The NEOGLI study has been submitted to further support the current application. The NEOGLI study was a phase 2 study performed at the Necker University Hospital, a public hospital for children in Paris and involved 10 paediatric patients from birth to less than 18 years of age with neonatal diabetes caused by a genetic mutation of KCNJ11 or ABCC8.

At inclusion (M0), all patients were treated with the classical form of glibenclamide (tablet or crushed tablet). After 1 month (M1), they were switched to the glibenclamide oral suspension formulation. At visits M1, M2 (after 2 months), and M4 (after 4 months), patients were hospitalized for clinical and laboratory examinations

Ten patients (7 boys) with KCNJ11 mutations, median age 2.7 years (0.3 to 16.2), median duration of glibenclamide therapy 2.3 years (0.01 to 11.3) were included. There were 6 children younger than 5 years old and 4 children over 5 years old.

After switching from glibenclamide tablets to glibenclamide oral suspension, there was no deterioration in glycaemic control as evident from the similar serum HbA1c (6.48 vs 6.1% at Visits M0 and M4, respectively; p=0.076) and serum fructosamine (283.4 vs 271.2 µmol/L at Visits M0 and M4, respectively; p=0.552) 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 $\leq$ 5.6% or an increase of HbA1c by >0.5% in patients with baseline HbA1c >5.6%.

The NEOGLI study also showed that - according to the hedonic scale assessment – the 6 children younger than 5 years old positively rated the acceptability of glibenclamide oral suspension. Five out of 6 parents of younger children preferred the suspension over the tablets. All 4 older children and their parents preferred the tablets over the suspension.

Discussion on clinical efficacy

Glibenclamide is in clinical use for more than 40 years in adults with type 2 diabetes mellitus. With this application a new oral suspension of glibenclamide is introduced for the treatment of NDM in children. The aim is to avoid the currently practised off-label use of crushed glibenclamide tablets.

This hybrid application is supported by data published in literature as well as by a distinct study performed in ten patients with NDM (NEOGLI) aiming at demonstration of efficacy, safety and acceptability of the glibenclamide suspension, which was designed in line with the recommendations of the PDCO (EMEA-001324-PIP01-12-M01).

In the evaluation of clinical benefit, the concept of targeting the underlying pathophysiology of NDM with glibenclamide is considered of key importance. This subtype of NDM is originating from overactive K_{ATP}-channels due to gene mutations. This overactivity can be treated specifically with the K_{ATP}-channel blocker glibenclamide.

Efficacy parameters reported in literature and investigated in the NEOGLI study focussed on 1) the investigation of glycemic control (HbA1c) after switching from insulin to glibenclamide (crushed) tablets or from glibenclamide crushed tablets to glibenclamide oral suspension 2) neurodevelopmental aspects and 3) the acceptability of the new formulation by infants and care givers.

The proof of concept in humans and especially in children for the use of oral glibenclamide in the treatment of NDM has been established in the years from 2004 to 2006 in several publications. Subsequently, many patients have now been transferred to sulfonylurea drugs (off label use). Successful transfer from insulin to glibenclamide was described in the literature for more than 200 patients. The response rate of NDM originating from overactive K_{ATP}-channels due to gene mutations has been described to be about 90%, depending on the type of the mutation. There is some evidence that a shorter diabetes duration is associated with a more successful transfer to sulfonylureas. Summarizing the data in the literature, HbA_{1c} values fell from ~8 % before transition to ~6% with SU therapy. The doses of SU required were high (typically 0.2 - 0.5 mg/kg/d of glibenclamide) when compared to doses used in adults with type 2 diabetes. The glibenclamide dose needed depended on the type of the mutation and the age of the patient at the time of the transfer,

with higher doses required at higher age. Frequently, a decrease of the dose (in mg/kg/d) required for maintenance of glycemic control has been observed with continuing SU-therapy. Only limited data on long term efficacy of sulfonylurea therapy of NDM are available which is acceptable for a rare disease.

Developmental impairments associated with K_{ATP}-channel mutations leading to NDM are frequently observed. It has been reported that SU therapy in neonatal diabetes secondary to mutations in potassium-channel subunits produces measurable improvements in neuropsychomotor impairments. As insulin therapy is without any effect here, an additional benefit may be considered plausible. However, the underlying pathophysiology (involved anatomical structures, responsible K_{ATP}-channel subtype) is unclear. Glibenclamide most probably does not enter the CNS which argues against an effect in the brain. However, the GlidKir study conducted in France with 18 patients has suggested that SU therapy improves neurodevelopmental parameters in patients with NDM owing to K_{ATP}-channel mutations. However, this study was uncontrolled. No final conclusion with respect to an additional clinical benefit of glibenclamide therapy can be drawn from this study.

For treatment of NDM in newborns, infants and children, glibenclamide crushed tablets are in current practice suspended in water. This mode of administration is considered rather inaccurate and can lead to errors in administration in newborns and infants. To overcome the obvious inconvenience of this process and in view of a better compliance, an oral glibenclamide suspension presented in two strengths (0.6 mg/ml and 6 mg/ml) has been developed.

The **NEOGLI-study** showed that acceptability of glibenclamide oral suspension was positively rated by patients and their parents. The glycaemic control was essentially unchanged after switching from glibenclamide (crushed) tablets to glibenclamide oral suspension.

In the published studies, which support this application, as well as in the NEOGLI-study only patients with approved mutations in the genes coding for the β-cell K_{ATP}-channel were included. In addition a small number of patients with chromosome 6q24-related transient neonatal diabetes mellitus were successfully treated. No data have been provided for patients with NDM of other origin, in which efficacy is physiologically unlikely.

On day180 of the procedure the applicant proposed an amended wording of SmPC section 4.1 (addition of “and adolescents” to the target population).

This wording was found to be not acceptable, since adolescents are not in need of the suspension formulation and the acceptability of the suspension formulation has been rated as poor by the patients and caregivers for patients above the age of 5. With the response to the day 180 LoQ, the Applicant consented to delete “and adolescents” from the wording in 4.1 and from corresponding sections in the product information**.**

Conclusion on clinical efficacy

In patients with certain mutations in the genes coding for the pancreatic beta-cell ATP-sensitive potassium channel, and chromosome 6q24-related transient neonatal diabetes, glibenclamide has been shown to be a targeted and efficacious treatment. The glibenclamide suspension applied for is considered to address an unmet medical need in newborns, infants and children with NDM. Compared to subcutaneous insulin therapy, this treatment targets the underlying condition more specifically. Glycaemic control seems to be improved with glibenclamide compared to insulin treatment. Acceptability of the new formulation by the patients and their care givers is also improved, at least for patients below the age of five. Albeit improvements of neuropsychomotor impairments have been shown in one study, the physiological rationale is less clear and conclusion on an additional benefit of neurodevelopmental improvement cannot be drawn at the present time.

2.4.5. Clinical safety

The review of safety of glibenclamide is based 1) on the analysis of adverse events reported in the studies analysed for efficacy of glibenclamide crushed tablets in neonatal diabetes (Babenko, 2006, Pearson, 2006, Beltrand, 2005 and Horeau, GENEODIA study 2016) and 2) the safety information reported in the NEOGLI study (Glibenclamide crushed tablets followed by oral suspension).

Patient exposure

According to a recently published retrospective analysis (Babiker et al., Diabetologia 59:1162-1166, 2016), 127 children and adolescents with neonatal diabetes were exposed to sulfonylureas.

Adverse events

Non-serious adverse events from studies published in the literature

Non-serious adverse events affecting the gastrointestinal tract (**transitory diarrhea**) were reported in literature (Pearson et al., 2006). The slightly higher number of **hypoglycaemic episodes** reported in the same study (2% with insulin compared to 5% with SU) during continuous glucose monitoring has to be seen in the light of the better glycemic control with SU treatment. No severe hypoglycaemic event was noted in this study. Treatment for a period for more than one year does not seem to affect growth in children aged between 1 and 12 years of age.

A longer-term observation published by Hoarau et al. showed no deterioration in renal or hepatic function and no cases of retinopathy or nephropathy. Insulin was re-introduced permanently in 1 patient (3 years after SU transfer) and transiently in another (1 year after transfer and during 4 years). A summary of the adverse events described in published literature is given in the following table:

Table 6 Safety information reported in studies analysed for efficacy of glibenclamide tablets or crushed tablets used in neonatal diabetes

Ref.	Number of Patients Indication	Study design Doses Study date	Safety information Reported SAE
Babenko, 2006	34 Patients with PND or TND	Electrophysiologic activity of mutant and wild-type K_{ATP} channels 0.2 mg/kg/day Glyburide crushed tablets Between 1995 and 2005	No safety information reported in the published data. Sulfonylurea is safe in the short term.
Pearson, 2006	49 Patients with diabetes due to Kir6.2 mutations (from 3 mths to 36 years)	Prospective multi-center study (France, Norway and UK) 0.1 to 0.2 mg/kg/day glyburide crushed tablets until 0.8 mg/kg/day 2005 study	Transitory diarrhea associated with abdominal pain No other side effects reported
Beltrand, 2015	19 included (18 treated; 1 withdrawn from parent decision not to switch to SU) Neonatal diabetes (aged from 0.1-18.5 years)	Prospective single-center study (Glidkir study, France) 0.2 mg/kg/day (range: 0-1.4) Glibenclamide crushed tablets From July 2006 to February 2009	No side effects reported
Hoarau, 2016	28 Neonatal diabetes	Long term Prospective study (GENEODIA Study) 0.16 mg/kg/day (range: 0.025 to 0.66) Median follow-up time 6.6 years (1.4 to 11.5 years).	No episodes of renal or hepatic failure and no development of retinopathy or nephropathy were reported. Insulin was re-introduced permanently in 1 patient (3 years after SU transfer) and transiently in another (1 year after transfer and during 4 years).

Non-serious adverse events in the NEOGLI study

Four patients experienced 10 NSAEs (**non serious adverse events**) considered as clinically important for the safety assessment (these adverse events had to be reported to the Sponsor). Of these, 7 NSAEs (abdominal pain, abdominal pain upper, diarrhoea, vomiting, and dyspepsia) were assessed as related to Glibenclamide. Most NSAEs were of mild intensity and all were resolved. Non-serious adverse events considered as clinically important for safety assessment and the numbers of patients involved are given in the following table:

Table 7 Non-serious adverse events considered as clinically important for the safety of assessment and number of patients involved during the study period

SOC and PT	Daonil		Glibentek	
	Events N	Patients involved N (%)	Events N	Patients involved N (%)
Gastrointestinal disorders	0	0	**8**	**3 (30%)**
- Abdominal pain	0	0	4	2 (20%)
- Abdominal pain upper	0	0	1	1 (10%)
- Diarrhoea	0	0	1	1 (10%)
- Dyspepsia	0	0	1	1 (10%)
- Vomiting	0	0	1	1 (10%)
Infections and infestations	**1**	**1 (10%)**	**1**	**1 (10%)**
- Gastroenteritis	1	1 (10%)	1	1 (10%)
Total	**1**	**1 (10%)**	**9**	**3 (30%)**

"Other" non-serious adverse events, which had to be described in the CRFs (but had not to be reported to the Sponsor) are given in the following table:

Table 8 Other non-serious adverse events and number of patients involved during the study period

SOC and PT	Daonil		Glibentek	
	Events N	Patients involved N (%)	Events N	Patients involved N (%)
Gastrointestinal disorders	**0**	**0**	**3**	**2 (20%)**
- Diarrhoea	0	0	1	1 (10%)
- Nausea	0	0	1	1 (10%)
- Toothache	0	0	1	1 (10%)
General disorders and administration site conditions	**2**	**1 (10%)**	**1**	**1 (10%)**
- Pyrexia	2	1 (10%)	1	1 (10%)
Infections and infestations	**3**	**3 (30%)**	**7**	**6 (60%)**
- Bronchiolitis	1	1 (10%)	0	0
- Bronchitis	1	1 (10%)	1	1 (10%)
- Laryngitis	1	1 (10%)	1	1 (10%)
- Nasopharyngitis	0	0	1	1 (10%)
- Otitis media acute	0	0	1	1 (10%)
- Pharyngitis	0	0	1	1 (10%)
- Rhinitis	0	0	2	2 (20%)
Metabolism and nutrition disorders	**0**	**0**	**8**	**5 (50%)**
- Hyperglycaemia	0	0	1	1 (10%)
- Hypoglycaemia	0	0	7	5 (50%)
Nervous system disorders	**0**	**0**	**5**	**3 (30%)**
- Headache	0	0	3	2 (20%)
- Migraine	0	0	2	1 (10%)
Reproductive system and breast disorders	**0**	**0**	**1**	**1 (10%)**
- Balanoposthitis	0	0	1	1 (10%)
Skin and subcutaneous tissue disorders	**0**	**0**	**1**	**1 (10%)**
- Acne	0	0	1	1 (10%)
Total	**5**	**4 (40%)**	**25**	**10 (100%)**

Gastrointestinal disorders were the most commonly reported NSAEs and are a known side effect of glibenclamide (for adults in the treatment of type 2 diabetes). This ADR is considered appropriately reflected in the proposed SmPC.

Frequencies of hypoglycaemia and hyperglycemia

The median frequencies of hypoglycaemic and hyperglycemic episodes are given in the following table:

Table 9 Frequency of hypoglycaemia and hypoglycaemia episodes

	M0 to M1[a]	M1 to M2	M2 to M4	M4 - M1[a]	
				difference	p value
% hypoglycaemia[b]					
Mean ± SD	3.34	2.92	1.63	-1.53	0.294
Median	1.30	2.10	1.45	-0.60	
Min	0	0	0	-9.50	
1st quartile	0	0.18	0.48	-1.90	
3rd quartile	6.10	4.55	2.35	0.40	
Max	11.50	9.00	4.40	2.40	
SD	4.09	3.14	1.48	3.49	
% hyperglycaemia[c]					
Mean ± SD	4.73	4.78	1.63	-3.09	0.418
Median	0	0.75	0.20	0	
Min	0	0	0	-15.70	
1st quartile	0	0	0	-3.40	
3rd quartile	3.80	1.88	1.38	0	
Max	22.80	39.40	7.10	6.30	
SD	8.44	12.21	2.73	7.49	

[a] *Data are missing for 1 patient*
[b] *Ratio of hypoglycaemia episodes and number of available blood glucose measurements*
[c] *Ratio of hyperglycaemia episodes and number of available blood glucose measurements*

The frequencies of hypoglycaemic and hyperglycemic episodes were similar when the treatment period on glibenclamide crushed tablets is compared to glibenclamide suspension. In this context, it has to be taken into account that the initial dose of glibenclamide was decreased by 21% for the 0.6 mg/ml suspension and by 14% for the 6 mg/ ml suspension due to the higher bioavailability of glibenclamide oral suspension.

Serious adverse event and deaths

Table 10 Safety information reported in NEOGLI study

Ref.	Number of Patients Indication	Study design Doses Study date	Safety information Reported SAE
NEOGLI	10 Neonatal diabetes (median age 2.7 years (0.3 to 16.2),	Open-label, uncontrolled, single arm study Acceptability and Tolerance study Glibenclamide tablets or crushed tablets (1 month) followed by oral suspension (3 months) Median dosage was 0.25 mg/k/day (0.08 - 0.77) before the switch and 0.12 mg/kg/day (0.06 to 0.56) 3 months after. From March 2015 to March 2016 Study currently continued with Extension protocol	2 SADR (Serious Adverse Drug Reaction): hypoglycemia 1 SAE: acute gastroenteritis

Laboratory findings

Results of laboratory assessments were within normal limits, except one patient with moderate anemia (haemoglobin, 8.20 g/dL) at baseline and one patient with slightly reduced neutrophils count and elevated transaminases at the study end. Physical examination at baseline and subsequent visits revealed no abnormalities, related to the study treatment. ECG results showed no clinically significant abnormalities.

Safety in special populations

No study data were generated in special populations other than in the paediatric population.

Recommendations given in section 4.2 of the proposed SmPC relating to children with renal and hepatic impairment are adequate, i.e. posology adjustment in patients with renal and hepatic impairment (mild to mderate) is stated in section 4.2 and section 4.4. Section 4.3 states that severe renal or hepatic impairment is a contraindication to glibenclamide treatment.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interactions studies of glibenclamide suspension have been performed. For drug interactions please refer to section PK/PD of this report.

Discontinuation due to adverse events

Not applicable

2.4.6. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.7. Discussion on clinical safety

The review of safety of glibenclamide is based on the analysis of adverse events reported in published studies investigating glibenclamide crushed tablets in neonatal diabetes (Babenko, 2006, Pearson, 2006, Beltrand, 2005 and Horeau, GENEODIA study 2016) and the safety information reported in the NEOGLI study (Glibenclamide crushed tablets followed by oral suspension). Of note, the frequencies of adverse drug reactions in this study cannot be directly compared due to the different study duration (1 month on Daonil crushed tablets and 3 month on glibenclamide suspension).

According to a recently published retrospective analysis (Babiker et al., Diabetologia 59:1162-1166, 2016), the exposure of children/adolescents with neonatal diabetes to sulfonylureas was 127. However, it is considered difficult to provide an exact number. Taking into account the rarity of the condition, the number of children exposed to glibenclamide, either as crushed tablets or as oral suspension is considered acceptable.

The study published by Pearson et al. reported five cases of transitory diarrhea. No other adverse drug reactions were reported in the published studies. Gastrointestinal side effects are a known ADR in adults. The proposed labelling in section 4.8 of the SmPC is adequate.

Except one patient with elevated transaminases and slightly reduced neutrophil count (both adverse drug reactions are labelled in the product information), laboratory parameters were without abnormalities. The frequency of **hypo- and hyperglycemia** under the treatment with glibenclamide suspension was investigated in the published study of Pearson et al. (comparison with the period in which patients received insulin) and in the NEOGLI study (comparison with the period in which patients received crushed glibenclamide tablets). Results of hyoglycemic episodes in the study of Pearson did not suggest an increased risk for hypoglycaemia/hyperglycemia after switching from insulin (median percentages of measurements with blood glucose below 3.3 mmol/L: 2% with insulin and 5% with glibenclamide). The results have to be viewed in the light of an overall better glycemic control. In the NEOGLI study, 7 non-serious hyoglycemic events were reported in 5 patients with glibenclamide suspension. With the Applicant`s Response it was clarified, that asymptomatic hypoglycaemia (non-severe) was over-reported after the switch to glibenclamide suspension. Actually, there were more cases of asymptomatic hypoglycaemia with glibenclamide crushed tablets.

Longer-term effects were assessed in the study of Pearson et al.: these1 year data showed no detrimental effect on growth compared with an age-matched population (no other parameter investigated). In the GENEODIA study (prospective analysis) no episodes of renal and hepatic failure and no development of

retinopathy or nephropathy were reported. In NEOGLI, five patients entered the extension phase; no adverse events likely to be related to study drug occurred during this extension period.

2.4.8. Conclusions on clinical safety

Glibenclamide is a well-known drug in the treatment of adults with type 2 diabetes mellitus and the safety profile in the adult population is well characterised. The majority of children exposed to Glibenclamide have been treated with crushed tablets, a mode of administration which may easily lead to over-or underdosing. The adverse drug reactions reported with crushed tablets mainly were mild in intensity and were resolved. The data available for the glibenclamide suspension are sparse and uncontrolled. This is acceptable for a rare disorder and based on the vast accumulated knowledge obtained in adults. No unexpected adverse drug reaction occurred.

2.5. Risk Management Plan

Safety concerns

Table 11

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

Pharmacovigilance plan

There are no planned additional pharmacovigilance activities in the RMP. Routine pharmacovigilance is considered sufficient to further characterise all safety concerns included in the RMP.

Risk minimisation measures

Table 12

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypoglycaemia	Text in SPC Dose adjustment to limit occurrence of hypoglycaemia is indicated in section 4.2. Warnings in section 4.4 indicate the risk, symptoms of occurrence and measure to be taken in such situation. Interaction that may lead to hypoglycaemia are indicated in section 4.5 with monitoring needed. Listed in section 4.8. Prescription only medicine. Text in PIL Handling of hypoglycaemia described in Warning and precautions in section 2 of the PIL	None
Transitory increased transaminases	Text in SmPC Listed in section 4.8. Text in PIL Listed in section 4. Other routine risk minimisation measures Prescription only medicine	None
Overdosing preservative sodium benzoate	Text in SmPC Table to determine correct dosage according to patient's weight and avoid overdosing is indicated in section 4.2 Warnings in section 4.4 indicate the amount of benzoate salt per each mL of product and symptoms of occurrence Text in PIL Risk is described in the section Warnings and precautions	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other routine risk minimisation measures Prescription only medicine	
Neutropenia	Text in SmPC Listed in section 4.8. Text in PIL Listed in section 4. Other routine risk minimisation measures Prescription only medicine	None
Bullous eruptions, exfoliative dermatitis, erythema multiforme	Text in SmPC Listed in section 4.8. Text in PIL Listed in section 4. Other routine risk minimisation measures Prescription only medicine	None
Anaphylactic reaction including dyspnoea, hypotension and shock	Text in SmPC Listed in section 4.8. Text in PIL Listed in section 4.and mentioned to present to emergency department Other routine risk minimisation measures Prescription only medicine	None
Hypoglycaemia due to mix ups of the different presentations	Text in SmPC Prescription instructions described in section 4.2 Text in PIL Section 3 How to give Amglidia Other routine risk minimisation measures The dosage will be clearly identified on the outer carton by two different colours: reverse type yellow for 0.6mg/ml and reverse type purple for 6mg/ml.	Educational material

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The syringe will be clearly identified on the outer carton. Indeed, a drawing of the two syringes (1 ml and 5 ml) will be present on the outer carton and the drawing of the syringe not available in the presentation will be crossed. In the case where a switch of presentations is necessary, the parents will be requested to bring back the old package. Syringes of respectively 1 mL and 5 mL will be clearly distinguishable. 1 mL oral syringe is thin and small while 5 mL syringe is thick and long. This will be fully described in both SPC and PL and should avoid the risk of using the wrong syringe.	
Patients with renal or hepatic impairment	Text in SmPC Posology adjustment in patient with renal and hepatic impairment is stated in section 4.2 and section 4.4. Section 4.3 indicates that serious renal or hepatic impairment is a contraindication to glibenclamide treatment. Text in PIL Section 2. Warning and precautions states that parents should tell their doctor if their child suffers from renal or hepatic disorders. Other routine risk minimisation measures Prescription only medicine	None
Long-term use	Text in SmPC Current clinical data about long-term use of glibenclamide are listed in section 5.1.	None

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that additional risk minimisation activities (educational material), such as a **prescriber's guide**, which aims at increasing awareness about the four presentations available (two strengths of the product, each containing either a 1mL or a 5mL syringe) and at minimising the risk of hypoglycaemia in case of mix-ups of the different presentations, are required in addition to the information included in the product information to this effect. The agreed key elements of this prescriber's guide can be found in section 4. Recommendation.

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the fact the fact that Amglidia is authorised as a new finished product formulation and considering the risk of medication errors linked to the different presentations, the CHMP is of the opinion that a separate entry in the EURD list for Amglidia is needed, as it cannot follow the already existing entry for glibenclamide. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk assessment

3.1. Therapeutic Context

Amglidia oral suspension is a new formulation of a well-known hypoglycaemic drug substance, ie. glibenclamide. Sulfonylureas such as glibenclamide are approved for the treatment of adult patients with type 2 diabetes. Glibenclamide has been widely used throughout the world since the year 1970. Therefore, vast knowledge on its efficacy and safety profile in adult patients with type 2 diabetes exists. More recently, sulfonylureas are used off-label, e.g. as crushed tablets, for the treatment of neonatal diabetes mellitus (NDM). Amglidia oral suspension is proposed for the treatment of neonatal diabetes mellitus, for use in newborns, infants and children.

Glibenclamide is a hypoglycaemic agent belonging to the class of sulfonylureas acting on the potassium channels of the pancreatic β-cells. The target disease for glibenclamide oral suspension is a form of neonatal diabetes mellitus associated with a defect of β-cell function with early onset in childhood that was recognized quite recently in the last 12 years. Specific genetic alterations, which explain the hyperglycemia, have been uncovered, showing that NDM is a new disorder with a rare incidence. Glibenclamide oral suspension is specifically designed to treat children with this rare condition for whom there is a lack of a suitable sulfonylurea formulation.

3.1.1. Disease or condition

Neonatal diabetes mellitus is a disease of early infancy. In approximately 50% the disease is due to mutations in the genes coding for the Kir6.2 and SUR1 subunits of the pancreatic β-cell ATP-sensitive potassium channel which result in failure of insulin secretion. Furthermore, the risk linked to NDM is also a risk of neurological and neuropsychological disturbances, including epilepsy leading to death or mental retardation as well as milder forms of dyspraxia or hypotonia. The condition was estimated to affect less than 0.2 in 10000 persons.

Amglidia 0.6 mg/ml and 6 mg/ml, oral suspension is proposed (by the applicant) to be administered in the following 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."

3.1.2. Available therapies and unmet medical need

Neonatal diabetes mellitus is a detectable condition that needs most often emergency treatment with intravenous fluid and insulin, the only method so far to re-establish metabolic control, and to avoid short-term risks such a ketoacidosis, dehydration and death in newborns and toddlers.

Insulin is difficult to handle because of the very low weight in these small children. The therapeutic margins are low between hypoglycaemia and hyperglycaemia, both harmful to the neurological development of the newborn.

Currently, in clinical practice sulfonylurea like glibenclamide are administered off-label or within clinical research protocols to newborns/children using a commercially available tablet form licensed for adults. To render the drug suitable for oral intake by newborns/children, the nursing staff, under medical prescription, or the parents at home, must crush the tablet into small pieces and present the drug to the infant by mixing the fragments with a small volume of water; the mixture is then administered with an oral syringe. The use of such formulation is not adequate as it is rather inaccurate and can lead to errors in administration in newborns and infants.

The development of the oral suspension for the treatment of NDM in newborns, infants and children to take the place of crushed tablets previously used off-label and insulin is considered to address an unmet medical need.

3.1.3. Main clinical studies

This hybrid application is based on data from studies published in literature and on data from the NEOGLI study (submitted as clinical study report). No controlled studies were performed in children with NDM, which is acceptable in the light of the rarity of the condition and due to ethical constraints.

Two papers published in 2006 (Babenko et al., Pearson et al.) have established the proof of concept of oral glibenclamide in the treatment of children with NDM with the use of crushed tablets instead of insulin injections. In these studies, 34 patients (age range 4.8 to 16.5 years, Babenko et al.) and 49 patients (age range 3 month to 36 years, Pearson et al.) had been investigated open-label. In both studies metabolic control (HbA1c) was investigated after switch from insulin to sulfonylureas.

In the study published by **Rafig** et al. (2008) 27 patients with SUR1 mutations were followed for at least 2 months after transfer from insulin to sulfonylureas. Information on clinical features, treatment before and after transfer, and the transfer protocol used was collected. Successful and unsuccessful transfer patients and glycaemic control before and after transfer were compared.

In the study published by **Babiker** et al. (2016) clinical data on 127 patients with neonatal diabetes due to KCNJ11 (Kir6.2) mutations who attempted to transfer to sulfonylureas were retrospectively analyzed. Successful transfer was considered when patients completely discontinued insulin whilst on sulfonylureas. All unsuccessful transfers received ≥0.8 mg kg^{-1} day^{-1} glibenclamide (or the equivalent) for >4 weeks.

Thurber et al. (2015) performed a retrospective cohort study using data on 58 individuals with neonatal diabetes due to KCNJ11 mutations. They assessed the influence of age (2.6 (0.0–33.6) years) at initiation of SU therapy on treatment outcomes.

The **GlidKir** study was an open-label study which has been performed to assess continuously the capillary glycaemia for three consecutive days and evaluate the insulin secretion under insulin and sulfonylureas and to evaluate the potential effects of sulfonylureas on neurodevelopmental parameters, which are known to be unresponsive to insulin in patients with neonatal diabetes owing to K_{ATP} channel mutations. In this prospective, open-label, single-center, single arm, non-randomized, uncontrolled study 18 patients (aged from 0.1-18.5 years) with neonatal diabetes and mutations in the beta cell potassium channel have been switched from insulin injections to glibenclamide (**Beltrand,** 2015).

The **NEOGLI study** evaluated efficacy, tolerance and acceptability of glibenclamide 0.6 mg/ml and 6 mg/ml oral suspension in patients suffering from diabetes mellitus secondary to a mutation of the ATP-dependent potassium channels. In this single-center, uncontrolled, non-randomised, open-label, prospective phase II study, 10 patients (aged from 0.3 – 16.2 years) with NDM and mutations in the beta cell potassium channel were switched from glibenclamide crushed tablets to Glibenclamide 0.6 mg/ml and 6 mg/ml oral suspension.

The GENEODIA study (**Hoarau**, 2016) was a long-term prospective follow-up study investigating metabolic control in children transferred from insulin to oral glibenclamide.

3.2. Favourable effects

The sulfonylurea glibenclamide is an antidiabetic drug in widespread clinical use for treatment of type 2 diabetes mellitus for more than 40 years. In the treatment of NDM with glibenclamide there is off-label clinical experience for more than 10 years.

The mode of action of oral glibenclamide specifically targeting the condition is clearly a favourable effect. The pharmacologic response to sulfonylureas seems to result from the closing of mutant K_{ATP} channels, thereby increasing insulin secretion in response to incretins and increased blood glucose levels.

As a consequence, insulin can be reduced or eliminated in affected patients, which is considered a benefit. Oral glibenclamide is more convenient to administer. About 90 % of the patients with NDM originating from overactive K_{ATP}-channels due to gene mutations can be transferred from subcutaneous insulin to sulfonylurea treatment. Successful transfer was described in the literature for more than 210 patients. In addition, efficacy of glibenclamide has also been reported in patients with 6q24-related transient ND.

As for any antihyperglycemic agent, improvement of metabolic control is clearly a benefit. Results from published literature show beneficial antihyperglycemic effects when patients were transferred from insulin to (crushed) sulfonylurea tablets (e.g. Rafiq et al. 2008, n = 23; Thurber et al. 2015, n = 48; Babiker et al. 2016, n = 112). HbA_{1c} was reduced in these studies by 1.5 %, 2.3 % and 2.3 %, respectively. In the Glidkir study (Beltrand et al. 2015) HbA_{1c} was reduced by 1.55 %. Only uncontrolled data are available; however consistent effects on HbA_{1c} across studies and the magnitude of the observed reduction are considered sufficient to conclude on a favourable metabolic effect in the short-term. Limited 10-year data suggest long-term efficacy.

Developmental impairments associated with K_{ATP}-channel mutations in the brain in patients with NDM have been frequently observed. As insulin is without any effect here, an additional benefit of glibenclamide treatment seems plausible. Reports from uncontrolled studies (Mlynarski et al, 2007, Beltrand et al. 2015), suggest improvements in neuropsychomotor impairments (uncertainties surrounding this issue are mentioned below in 3.3.).

The NEOGLI study showed that children with NDM can be effectively and safely switched from crushed non-micronised tablets to the oral suspension of glibenclamide. Results of the NEOGLI study also showed that acceptability of glibenclamide oral suspension was positively rated by the target patient population, i.e., patients younger than 5 years old (n = 6). In addition, their parents preferred the suspension over the tablets.

3.3. Uncertainties and limitations about favourable effects

Insulin does not affect developmental impairments frequently associated with NDM. Pathophysiological background of these impairments is unclear with respect to tissues and K_{ATP}-channel subtypes involved. It has been reported in literature, that SU therapy in NDM secondary to mutations in potassium-channel subunits produces measurable improvements in neuropsychomotor impairments. However, results of the GlidKir study do not allow for a firm conclusion on an improvement of neuropsychological disturbances because of its uncontrolled nature and due to the fact that neurodevelopmental changes are inherent in a child`s development. In addition, it is unclear whether sulfonylureas do cross the blood-brain-barrier. Therefore, no final conclusion with respect to a clinical benefit of a glibenclamide therapy regarding neurodevelopmental improvements can be drawn and no such benefit can be claimed.

Bibliographical evidence and the NEOGLI-study included only patients with confirmed mutations in the genes coding for the β-cell KATP-channel. In addition, a small number of patients with chromosome 6q24-related transient neonatal diabetes mellitus were successfully treated. Extrapolation to NDM due to other mutations is not possible.

In persistent NDM, a life-time treatment has to be expected. Long-term data arguing for a persistent beneficial effect of SU in NDM are very limited. In 11 patients with KCNJ11-associated PNDM, retained HbA_{1c} control with SU for more than 57 month was reported. Additional preliminary data suggest that efficacy is maintained for at least 10 years. In the light of the sparse long-term data, no firm conclusion is possible on whether life-long efficacy of glibenclamide can be expected. This awareness is important in the management of patients with the disease.

3.4. Unfavourable effects

The safety experience in young patients with NDM is limited. The ADR profile appears to be in line with that observed in adults. Side effects which occurred in children with NDM were hypoglycaemia (two severe, drug-related cases in the NEOGLI study, 7 cases classified as non-severe with uncertain drug relation), gastrointestinal disorders and laboratory abnormalities (one case of elevated transaminases, one case of neutropenia). All side effects resolved without sequelae. No unexpected ADR occurred.

With respect to hypoglycaemia, one study compared glibenclamide to insulin (Pearson et al., 2006) and found 2% of measurements of capillary blood glucose below 3.3 mmol/L with insulin compared to 5% with glibenclamide. However, these results have to be interpreted in the light of a better glycemic control with glibenclamide. No other comparative data on the incidence of hypoglycaemia are available.

In the NEOGLI study episodes of hypoglycaemia were comparable with glibenclamide crushed tablets and glibenclamide suspension.

3.5. Uncertainties and limitations about unfavourable effects

No clinical data exist with respect to the potential impact of glibenclamide on growth and development. However, considering the mechanism of action of glibenclamide, no detrimental effects are expected. No data are available for children with impaired renal or hepatic function; however, treatment recommendations in the proposed SmPC for these special groups are considered adequate (contraindication for severe renal and hepatic impairment, warnings for children with mild and moderate hepatic impairment).

3.6. Effects Table

Table 13 Effects Table for Glibenclamide oral suspension.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Antihyperglycemic effect	A total of 44 patients (90 percent) successfully discontinued insulin after receiving sulfonylureas. HbA_{1c} improved in all patients who switched to sulfonylurea therapy (from 8.1 percent before treatment to 6.4 percent after 12 weeks of treatment).	N/A	Sulfonylureas after transfer 0.45 mg/kg/day (range 0.05 to 1.5 mg/kg/day)	No control	Uncontrolled study from bibliographic source. It is assumed, that the patients are evaluated in the study from Babiker et al. (2016) again.	Pearson et al. 2006
	Twenty-three patients (85%) with SUR1 mutations successfully transferred onto sulfonylureas. Median HbA1C fell from 7.2% (interquartile range 6.6–8.2%) on insulin to 5.5% (5.3–6.2%) on sulfonylureas	N/A	Sulfonylureas after transfer 0.26 mg/kg/day (range 0.07 to 2.80 mg/kg/day)	No control	Uncontrolled study from bibliographic source.	Rafiq et al. 2008

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	48 (from 58) patients with Kir6.2 mutations could be transitioned from insulin to glibenclamide monotherapy. HbA1c fell from an average of 8.5% before transition to 6.2% after SU therapy. Age of initiation of SU correlated with the dose (mg kg^{-1} day^{-1}) of SU required at follow-up.	N/A	Sulfonylureas	No control	Uncontrolled study from bibliographic source.	Thurber et al. 2015
	112 out of 127 (88%) patients with Kir6.2 mutations successfully transferred to sulfonylureas from insulin with an improvement in HbA1c from 8.2% on insulin, to 5.9% on sulphonylureas.	N/A	Sulfonylureas	No control	Uncontrolled study from bibliographic source.	Babiker et al. 2016
	The glycaemic control was essentially unchanged after switching from glibenclamide (crushed) tablets to glibenclamide oral suspension.	N/A	Amglidia (suspension)	No control		NEOGLI study

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Neurodevelopmental effect	SU improved hypotonia (in 12 of 15 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).	N/A	Glibenclamide after 12 month 0.2 mg/kg/day (range 0 to 1.43 mg/kg/day)	No control	Uncontrolled study from bibliographic source. Only 18 patients were evaluated. The subjects included were very heterogeneous in respect to age (0.1–18.5 years), type of mutation and severity of impairment.	Glidkir study, Beltrand et al. 2015
Acceptability	Acceptability of glibenclamide oral suspension was positively rated by the target patient population, i.e., patients younger than 5 years old (n = 6). In addition, their parents preferred the suspension over the tablets.	N/A	Glibenclamide Pharma Services (suspension)	No control	Prospective study; formulation applied for has been investigated	NEOGLI study
Unfavourable Effects						
Hypoglycaemia	2 serious adverse drug reactions (NEOGLI study); both events resolved without sequelae; overall, 7 events of hypoglycaemia.	N/A	Glibenclamide oral suspension; dose in patient 000-2: 0.7 mg/day dose in patient 000-9: 4.8 mg/day	No control		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Gastrointestinal disorders	1 serious case of gastroenteritis (not related to study treatment) 7 NSAEs (abdominal pain, abdominal pain upper, diarrhoea, vomiting, dyspepsia) NEOGLI study; 5 cases of transitory diarrhoea (Pearson)	N/A	Glibenclamide crushed tablet or oral suspension	No control	Labelled, no uncertainties	
Laboratory abnormalities	1 case of increased transaminases; 1 case of neutropenia	N/A	Glibenclamide suspension	No control	Neutropenia and elevated transaminases are labelled in the updated SmPC	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The ability of oral glibenclamide to specifically address the underlying pathophysiology in children with NDM is seen as a benefit per se. As a consequence, insulin can be reduced or eliminated in the neonates, infants and children, which is considered an important benefit since oral glibenclamide is more convenient to administer. About 90 % of the patients with NDM originating from overactive K_{ATP}-channels due to gene mutations can be transferred from subcutaneous insulin to sulfonylurea treatment. Successful transfer was described in the literature for more than 210 patients. In addition, efficacy of glibenclamide has also been reported in patients with 6q24-related transient ND.

As for any antihyperglycemic agent, metabolic control is key for assessment of efficacy. Results from published literature show beneficial antihyperglycemic effects when patients were transferred from insulin to (crushed) sulfonylurea tablets (e.g. Rafiq et al. 2008, n = 23; Thurber et al. 2015, n = 48; Babiker et al. 2016, n = 112). HbA_{1c} was reduced in these studies by 1.5 %, 2.3 % and 2.3 %, respectively. In the Glidkir study (Beltrand et al. 2015) HbA_{1c} was reduced by 1.55 %. Although only uncontrolled data are available, the consistent effects on HbA1c across studies and the magnitude of the observed reduction are considered sufficient to conclude on a favourable metabolic effect in the short-term. Limited literature data support long-term efficacy of glibenclamide in patients with NDM and an amenable mutation.

Acceptability of the newly developed suspension formulation is also considered highly relevant in paediatric patients. The positive rating of acceptability by patients and care givers in children below the age of 5 in the NEOGLI study is reassuring. The development of an age-appropriate formulation is considered a benefit and expected to simplify treatment, increase dose accuracy and potentially increase compliance.

Hypoglycaemia is considered the most relevant side effect since it may impair the child`s long term development. Comparative data as regards hypoglycaemia (Pearson et al.) do not allow for any firm conclusion on the relative risk of hypoglycaemia of glibenclamide compared to insulin. In the NEOGLI study the frequency of hypoglycaemia with glibenclamide crushed tablets and glibenclamide suspension were comparable.

Gastrointestinal side effects are transient and the observed cases were mild in nature and resolved without sequelae, albeit they may temporarily impair the patient`s and care giver`s quality of life. Overall, the safety profile appears to be in line with that observed in adults with type 2 diabetes. No unexpected side effects occurred. The safety issues, most importantly hypoglycaemia, are expected to be well manageable in clinical practice.

3.8. Balance of benefits and risks

Specifically targeting the underlying pathophysiology of NDM in patients with mutations in the KATP-channel and a better glycemic control compared to insulin is a clear benefit of glibenclamide. In addition, efficacy has also been reported in patients with rare 6q24-related transient ND. The safety profile of glibenclamide in patients with NDM is in line with that known in adults and adverse drug reactions reported in NEOGLI and the literature were generally mild and are considered well-manageable in clinical practice.

Therefore, the benefits of the oral formulation of glibenclamide are considered to outweigh the risks in the treatment of newborns, infants and children with NDM and an amenable mutation.

3.9. Additional considerations on the benefit-risk balance

This application concerns a hybrid version of glibenclamide developed as a suspension formulation for use in children. The reference product Daonil tablets is indicated for *non insulin dependent (type 2 diabetes mellitus), whenever blood glucose levels cannot be controlled adequately by diet, physical exercise, and weight reduction alone.*

The clinical pharmacology and PK/PD approach of this Article 10.3 hybrid application was considered acceptable for the extreme rare disease of neonatal diabetes. The 1AMK1/Glibentek1 study was designed to investigate the relative bioavailability of the two glibenclamide suspensions (0.6 mg/ml and 6 mg/ml) versus crushed tablets of the reference product Daonil® 5 mg in healthy male subjects. A higher bioavailability was found for the oral suspension compared to glibenclamide crushed tablets (non-micronized). Dosing recommendations and guidance for transfer of patients with neonatal diabetes from off-label use of glibenclamide tablets to glibenclamide suspension are provided in the respective sections of the SmPC. The SmPC also clarifies that no dose recommendation can be given for switching patients from micronized glibenclamid tablets to Amglidia.

From a risk minimisation perspective, the provision of an educational material such as a prescriber's guide, which will be attached to the Product Information, will increase awareness about the four presentations available (two strengths of the product, each containing either a 1mL or a 5mL syringe) and minimise the risk of hypoglycaemia in case of mix-ups of the different presentations, at the time of prescription.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Amglidia is favourable in the following 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The 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 presentations available (two strengths of the product, each containing either a 1mL or a 5mL syringe) and at minimising the risk of hypoglycaemia in case of mix-ups of the different presentations.**

The MAH shall ensure that, in each Member State where Amglidia is marketed, all healthcare professionals who are expected to prescribe Amglidia, have access to the following educational guide:

- A Prescriber's Guide, including the SmPC of Amglidia attached

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

Amglidia is a suspension to be administered with a provided oral syringe graduated in mL. Healthcare professionals or patients should never use another syringe than the one provided in the box to avoid dosing errors which could result in serious harm.

- Amglidia is available in four different boxes corresponding to four different presentations (four different strengths):
  - One box for the 0.6 mg/mL strength with one 1mL syringe: yellow colour for outer carton and reverse type yellow colour for label
  - One box for the 0.6 mg/mL strength with one 5 mL syringe: yellow colour for outer carton and reverse type yellow colour for label
  - One box for the 6 mg/mL strength with one syringe of 1 mL: purple colour for outer carton and reverse type purple colour for label
  - One box for the 6 mg/mL strength with one syringe of 5 mL: purple colour for outer carton and reverse type purple colour for label

- The choice of the Amglidia strength should be defined according to the prescribed posology and the patient's body weight.

- The Amglidia 0.6 mg/mL strength should not be used for posology higher than 0.6 mg/kg/day to limit the exposure to the sodium benzoate excipient. Please read the posology and method of administration in the SmPC attached to this prescriber'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 1mL or below, the 1mL syringe should be prescribed;
    - ✓ If the volume per administration is more than 1mL, the 5mL syringe should be prescribed.

- The prescription should state the calculated daily dose in mL, the strength of Amglidia to be used, the number of administrations over which the daily dose is divided, as well as the volume in mL to be administered for each dose and the size of the syringe to be used.

- Patients and/or their caretakers should be explained that:
  - They are prescribed a dose of Amglidia in mL according to their body weight. This dose is to be administrated with a provided oral syringe graduated in mL.
  - There are 2 presentations for a same strength: one with a syringe of 1mL and one with a syringe of 5 mL.
  - Patients or their caretakers should be reminded to use the correct syringe as stated in their prescription.

- If the patient is prescribed a different presentation, the prescriber should highlight to the patient the packaging differences between the different presentations (focus on colour differentiation, warning statements on carton, thickness and length of the provided syringe).

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.