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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Sibnayal (tripotassium citrate monohydrate and potassium hydrogen carbonate)
Treatment of distal renal tubular acidosis
EU/3/17/1888

Sponsor: Advicenne

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Tripotassium citrate monohydrate and potassium hydrogen carbonate
Other name(s)	ADV7103
International Non-Proprietary Name	Potassium hydrogen carbonate Potassium citrate monohydrate
Tradename	Sibnayal
Orphan condition	Treatment of distal renal tubular acidosis
Sponsor's details:	Advicenne 22 Rue de La Paix 75002 Paris France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Advicenne
COMP opinion date	19 May 2017
EC decision date	20 June 2017
EC registration number	EU/3/17/1888
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	J. Lodewijk Hillege / T. Radimersky
Applicant	Advicenne
Application submission date	9 November 2019
Procedure start date	28 November 2019
Procedure number	EMEA/H/C/005407/0000
Invented name	Sibnayal
Proposed therapeutic indication	Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older. Further information on Sibnayal can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Sibnayal
CHMP opinion date	10 December 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E. J. Rook / L. Gaidadzi
Sponsor's report submission	25 March 2020
COMP discussion and adoption of list of questions	3 December 2020
Oral explanation	17 March 2021
Sponsor's removal request	18 March 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation was based on the following grounds:

The sponsor Advicenne S.A. submitted on 27 January 2017 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing tripotassium citrate monohydrate and potassium hydrogen carbonate for treatment of distal renal tubular acidosis (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing tripotassium citrate monohydrate and potassium hydrogen carbonate was considered justified based on preliminary clinical data showing restoration of serum bicarbonate levels in affected patients;
- the condition is chronically debilitating due to sensorineural hearing loss, restricted growth, rickets and nephrolithiasis and life threatening with mortality reported as high as approximately 10% for some groups of affected patients;
- the condition was estimated to be affecting approximately 2.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tripotassium citrate monohydrate and potassium hydrogen carbonate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that support restoration of serum bicarbonate levels, which compare favourably to existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

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

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

Condition

Distal renal tubular acidosis was the first type of RTA identified and is thus also known as type I RTA. It is characterized by impaired renal acid secretion, initially with normal glomerular filtration rate (GFR) causing hyperchloremic metabolic acidosis. This leads to the excretion of alkaline urine relative to systemic metabolic acidosis. Hypokalaemia is frequently associated with dRTA.

In its primary (inherited) form distal RTA is described as a rare disease in the literature (Palazzo Kidney Int 2017 Feb20) and is assumed to be caused by mutations in SLC4A1 (encoding an anion exchanger), ATP6V0A4 and ATP6V1B1 (subunits of H+ATPase). Two novel homozygous missense recessive mutations were identified recently in patients with dRTA: in FOXI1 that encodes a transcription factor important for acid-secreting epithelia (Enerbäck et al 2017), in WDR72 that is thought to be involved in intracellular trafficking potentially affecting targeting of acid-base regulatory proteins (Rungroj et al 2018). The phenotype of these 2 new mutations mimic the renal findings of patients with the first 3 identified mutations, and patients with FOXI1 present also with early-onset sensorineural deafness (Enerbäck et al 2017). The primary form of distal RTA may present with various degrees of severity and is usually detected in infants. Clinical features may include sensorineural hearing loss, vomiting, obtundation, restricted growth, rickets and nephrolithiasis. (Yaxley and Pirrone, 2016)

In addition to the primary form there are also secondary (acquired) forms that are usually seen in adults, and are secondary to autoimmune diseases (such as Sjogren and SLE), exposure to nephrotoxins (such as amphotericin B and lithium), but also other instances such as obstructive nephropathy, pyelonephritis, primary hyperparathyroidism, intravascular volume depletion and chronic kidney disease of any cause (Yaxley and Pirrone, 2016).

The approved therapeutic indication "treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older" falls within the scope of the designated orphan condition "treatment of distal renal tubular acidosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

However, in the final assessment report it is stated that a formal claim on non-inferiority and superiority cannot be made due to several issues on the robustness of the study design and conduct, such as the lack of titration of an optimal dose for standard of care (SoC) treatment, as a comparator and the sequential study design.

Chronically debilitating and/or life-threatening nature

There has been no change to the seriousness of the condition since the orphan designation in 2017.

The sponsor suggests that newly available data further substantiates and reinforce the prior findings on the chronically debilitating nature of dRTA, as it has been shown that without the adequate control of the metabolic acidosis, dRTA leads to kidney impairment as early as in childhood and absence of pubertal growth. If left untreated, dRTA is still considered a highly debilitating condition which can be life-threatening as it can irreversibly deteriorate renal function, weaken muscle strength, cause hearing loss, affect bone structure and result in adults of short stature.

At the time the condition was considered chronically debilitating due to sensorineural hearing loss, restricted growth, rickets and nephrolithiasis and life threatening with mortality reported as high as approximately 10% for some groups of affected patients.

Number of people affected or at risk

The sponsor performed a bibliographical search (general as well as orphan specific databases) in order to update the prevalence estimation of dRTA. Since the agreement on the prevalence of dRTA during

ADV7103 ODD assessment in June 2017, the sponsor found no new significant publications providing information to re-evaluate dRTA prevalence at the European level.

As the prevalence for dRTA is not known in total inherited and acquired dRTA were calculated separately:

- The sponsor used an estimation of the prevalence of inherited dRTA calculated from the available data.
- For acquired dRTA, the prevalence per underlying disease/aetiology was calculated from the available data using the prevalence of the underlying disease and an estimate of the proportion of patients within that disease with dRTA. A two-step approach was undertaken (calculation of the prevalence of the aetiology then the proportion of patients presenting dRTA within the aetiology).

As there were no new contributing factors the sponsor concludes on the same prevalence as for the orphan designation: The estimated prevalence for dRTA ranges from 0.699 to 2.14 per 10,000 persons and is considered unchanged at the time of this maintenance report submission, i.e. affecting no more than 2.1 per 10,000 persons in Europe. This estimate can be accepted at time of marketing authorisation as well.

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

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

Existing methods

No new treatment has been registered since the orphan designation, meaning that the same medicinal products and pharmacy/hospital compounded products which were detailed in the initial application are still in use to treat patients with dRTA, whether a child or an adult with an inherited or an acquired dRTA.

The sponsor has identified several alkalising salts being authorised in the EU for broader indications covering dRTA. These include immediate release product containing potassium citrate and potassium bicarbonate, each in different product combinations. There is also a modified release potassium citrate coated tablet (Acalka) authorised in Spain and Portugal for the treatment of (amongst others) renal lithiasis. The sponsor also confirms that there are pharmacy formulations reported to be used, containing the proposed active substances.

The products authorised for the treatment of "metabolic acidosis" can indeed be considered to cover the proposed target population for Sibnayal, because dRTA is a type of metabolic acidosis.

Significant benefit

According to the sponsor, the overall intent of ADV7103 development programme is to deliver the necessary alkali and potassium coverage with a twice-daily administration (morning and evening) using a formulation that has been specifically developed for patients with dRTA, including paediatric patients. This contrasts with various existing alkali therapies, which were not developed specifically for the dRTA patient population. These therapies, which are mostly immediate release formulations, are not able to provide the appropriate coverage without multiple intakes during the day and at night.

Multiple intakes are known to cause treatment compliance issues, which can negatively impact the management of the of dRTA (Kruse et al 1991; Claxton et al. 2001; Penfornis 2003).

The main arguments for significant benefit are:

1. Superior efficacy for the treatment of dRTA.

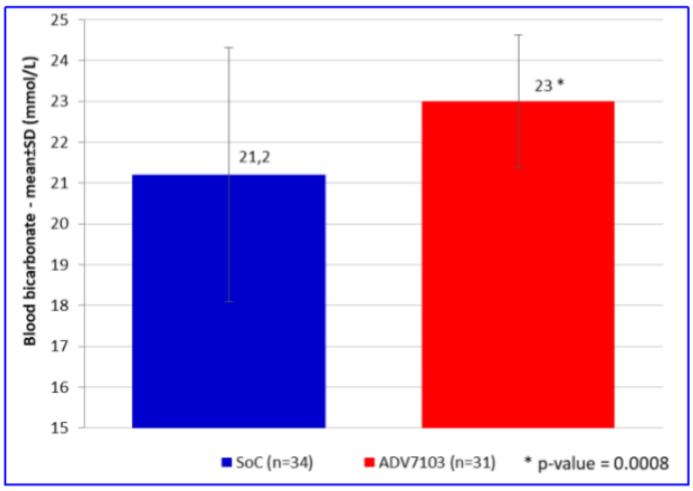
2. Improved product attributes/acceptability to treat dRTA (which contributes to the improved efficacy as well as a major contribution to patient care).

3. Improved standardisation of dRTA treatment.

To support these claims the sponsor refers to the results of Study B21CS. The study met its non-inferiority primary endpoint and the primary endpoint was then tested for superiority.

An improvement with normalisation of blood bicarbonate levels and less variability were reported with ADV7103 compared to SoC. This analysis showed a statistically significant (p-value = 0.0008) higher level of blood bicarbonate with treatment with ADV7103 compared to treatment with SoC, with a difference of 1.6 mmol/L (95% CI: 0.6679, 2.6034).

Average blood bicarbonate results ± SD in the overall ITT set in Study B21CS



Source: from Table 14.2.1.2 – B21CS

According to the sponsor, the primary endpoint associated non-responder analyses (non-responder patients with bicarbonateamia values below normal ranges) showed a superiority of ADV7103 compared to SoC based on the raw proportions that were also statistically significant.

Such assertions are to be considered with caution. The CHMP did not accept a formal claim on non-inferiority and superiority due to several issues on the robustness of the study design and conduct. For this reason, it cannot be claimed that there is a clinically relevant advantage over the alternative treatments (SoC).

A significant benefit based on a major contribution to patient care (improved product attributes/acceptability to treat dRTA) can only be discussed and accepted if the product has shown to have similar efficacy and safety as the recognised satisfactory methods, in this case the SoC. It also requires data to support it (e.g. PROs). As this has not been shown, a claim of significant benefit cannot be supported.

An improved standardisation of treatment would per se not be considered in support of a significant benefit as it does not translate into a measurable benefit for the patient.

The sponsor will be invited to further discuss the justification of significant benefit.

4. COMP list of issues

Significant benefit

The sponsor is requested to further justify the significant benefit, with any arguments, since a formal claim on non-inferiority and superiority versus standard of care has been dismissed by the CHMP. This was due to several issues on the robustness of the study design and conduct.