LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Natriumbikarbonat Abboxia
(sodium hydrogen carbonate)

Asp no: 2021-1034

This module reflects the scientific discussion for the approval of Natriumbikarbonat Abboxia. The procedure was finalised on 2022-09-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Natriumbikarbonat Abboxia, 50 mg/ml, solution for infusion.

The active substance is sodium hydrogen carbonate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Natriumbikarbonat Abboxia, 50 mg solution for infusion, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Abboxia AB applies for a marketing authorisation in Sweden through a National Procedure.

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of sodium bicarbonate are well known. As sodium bicarbonate is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Conclusions on studies:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sodium hydrogen carbonate is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence studies have been performed for the purpose of this application, which is acceptable. The product is an aqueous intravenous solution containing the same active substance as the currently authorised reference product in Sweden (Natriumbikarbonat Kabi Fresenius 50 mg/ml).

Natriumbikarbonat Abboxia, 50 mg solution for infusion is administered intravenously at a dose that depends on the severity of the acidosis and is monitored by the acid-base-status. Hence, the lack of discussions about exposure variability and PK in special populations is considered acceptable.

No formal drug-drug interaction studies have been performed, which is acceptable. Known interaction risks are described in the SmPC.

In conclusion, for this product, the provided clinical overview and its references are considered acceptable in terms of describing the pharmacokinetics of sodium bicarbonate.

Pharmacodynamics
Sodium bicarbonate has an alkalising effect in plasma by shifting the bicarbonate (HCO_3^-) to carbon dioxide (CO_2) ratio. Bicarbonate is the conjugate base component of the principal extracellular buffer in the body: the bicarbonate/carbonic acid buffer. The pH in plasma and interstitial fluid is maintained at an almost constant level between 7.37–7.42. Regulation of blood pH and, by extension, the entire extracellular fluid compartment depends on the interplay between three main systems:

1) the urinary system;
2) the neuro-respiratory systems;
3) extracellular buffers.

Among physiological buffers, the most powerful is the CO_2/ HCO_3^- buffer system.

The use of sodium bicarbonate to treat acidosis is firmly rooted in well-known acid-base physiology. It is, however, not self-evident that correction of acidosis using buffer solutions are beneficial for more patient-relevant downstream outcomes. The mainstay of therapy for patients with acidosis is treatments targeting the underlying cause.

Clinical efficacy
The use of sodium bicarbonate to treat acidosis is longstanding and firmly rooted in well-known acid-base physiology. It is, however, not self-evident that correction of acidosis using buffer solutions are beneficial for more patient-relevant downstream outcomes. The mainstay of therapy for patients with acidosis is clearly treatments targeting the underlying cause.

Regarding different types of acidosis, there is reasonable support for beneficial effects from treatment of ICU patients with severe acidaemia (pH ≤ 7.20), at least in the subpopulation with reduced renal function. It is also agreed that treatment with bicarbonate have support in international consensus guidelines (KDIGO 2012) for the management of patients with chronic kidney disease, and also in particular circumstances in acute kidney disease. Treatment with bicarbonate in diabetic ketoacidosis is not well supported by data, may be deleterious, and cannot be generally recommended.

During cardiopulmonary resuscitation there is according to international consensus guidelines no place for general use of bicarbonate, except for a possible role when there is co-existing hyperkalaemia, malignant hyperthermia, or some specific drug overdoses.

Clinical safety
The safety profile is considered well established in clinical practice since many decades. It has been sufficiently characterised, also based on general acid-base physiology and understanding of electrolyte disturbances, as reviewed in the submitted literature.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Natriumbikarbonat Abboxia.

Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

No important potential or identified risks, or missing information, are proposed for the RMP. This is appropriate. Sodium bicarbonate has been extensively used clinically for several decades. The safety profile is well characterized.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.1 signed 31 August 2021 is considered acceptable.

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 MPA;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was Swedish.

The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for *Natriumbikarbonat Abboxia, 50 mg/ml, solution for infusion* has been submitted according to Article 10a of Directive 2001/83/EC. The justification for well-stablished use according to Article 10a of directive 2001/83/EC should preferably be supported by data. Support can be provided from sales data, treatment guidelines, textbooks, review articles, and/or drug utilisation studies or surveys documenting well-stablished use within the EU for more than 10 years.

That a product has been approved for marketing authorisation does not automatically mean that it has been marketed and used to such an extent in routine care that it can be characterised as well-established. In this case, it is accepted that the submitted review articles and references made to treatment guidelines provide sufficient evidence to fulfil the above requirements.

Since it is a stand-alone application, efficacy and safety should be characterised based on published studies. For characterisation of the efficacy and safety, preference should be given to recent, well-designed studies with a low risk for bias and adequate sample size. Narrative reviews are of less relevance. If used, the supporting literature that is mentioned in the review, and that the Applicant wishes to refer to, should be provided as full text references and be critically discussed individually. For characterisation of safety also well-designed, comparative observational studies are relevant. The Applicant has submitted an up-to-date literature review with articles published as late as 2021.

The use of sodium bicarbonate to treat acidosis is longstanding and firmly rooted in well-known acid-base physiology. It is, however, not self-evident that correction of acidosis using buffer solutions are beneficial for more patient-relevant downstream outcomes. The clear mainstay of therapy for patients with acidosis is treatments targeting the underlying cause.

Regarding different types of acidosis, there is reasonable support for beneficial effects from treatment of ICU patients with severe acidaemia ($pH \leq 7.20$), at least in the subpopulation with reduced renal function. It is also agreed that treatment with bicarbonate have support in international consensus guidelines for the management of patients with chronic kidney disease, and also in particular circumstances in acute kidney disease. Treatment with bicarbonate in diabetic ketoacidosis is not well supported by data, may be deleterious, and cannot be generally recommended.

During cardiopulmonary resuscitation there is according to international consensus guidelines no place for general use of bicarbonate, except for a possible role when there is co-existing hyperkalaemia, malignant hyperthermia, or some specific drug overdoses.

There is consequently reasonable support for some limited parts of the initially proposed indications. By adding a cross-reference to section 4.2 and 5.1, where the limitations with this treatment are specified, and reference is made to established treatment guidelines, the indication becomes more up-to-date and in line with current clinical practice.

The characterisation of safety is overall agreed. The safety profile is considered well established in

clinical practice since many decades. It has been sufficiently characterised also with support from acid-base physiology and understanding of electrolyte disturbances, as reviewed in the submitted literature.

The benefit/risk relation of this product is beneficial.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Natriumbikarbonat Abboxia, 50 mg/ml, Solution for infusion was approved in the national procedure on 2022-09-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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