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Sodium Bicarbonate 500 mg Capsules

Redacted under section 40 of the Freedom of Information Act

MODULE 2.4

NONCLINICAL OVERVIEW

Prepared by [redacted]

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Contents

INTRODUCTION: PRODUCT PROFILE

a) Type of application

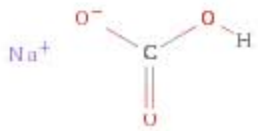
This application is made under Article 10 (1) of Directive 2001/83/EC, a generic application. Sodium bicarbonate has a well-established medicinal use with recognized efficacy and an acceptable level of safety. The original product has been marketed within the EEA for not less than 10 years. This non clinical review is based upon published literature.

b) Summary of properties

b)(i) Active substance; Sodium bicarbonate

Sodium bicarbonate complies with the requirements of the European Pharmacopoeia.

Chemical class	Inorganic salt
Molecular formula	$NaHCO_3$



Molecular weight	84
Chemical Name	Sodium bicarbonate, sodium hydrogen carbonate
CAS Registry Number	144-55-8
Appearance	White or almost white, crystalline powder.
Solubility	Soluble in water, practically insoluble in alcohol
Stereochemistry	Not relevant

c) Summary of kinetics

Bicarbonate forms CO_2 in the stomach and at normal doses this is mostly absorbed, together with remaining quantities of bicarbonate ion (in the stomach and small intestine) and sodium. The absorbed materials then enter the relevant body pools and bicarbonate contributes to acid-base homeostasis. Studies with ^{13}C or ^{14}C labelled bicarbonate have found that the majority of the label is eliminated as CO_2 in breath (probably about 80% or more). Very small amounts of label are eliminated in urine (1-2%) and faeces <0.5%). There is little difference in the quantitative elimination pattern of orally or intravenously administered bicarbonate or between various animal species and humans.

b)(ii) Finished product

The finished product is a hard gelatin capsule containing sodium bicarbonate 500mg.

d) Indications and dose

The product is intended for the treatment of dyspepsia. It may also be used to treat metabolic acidosis. For dyspepsia the dose is 1- 5g when required. In the case of metabolic acidosis the dose will depend on the acid-base balance and electrolyte status of the patient and must be calculated on an individual basis.

e) Precautions and contraindications

Large doses of bicarbonate could produce metabolic alkalosis. The sodium content could elevate blood pressure or contribute to fluid retention and pulmonary oedema. Hypokalaemia may be exacerbated. The product should be avoided in patients on salt-restricted diets and administered with caution in patients suffering from heart failure, hypertension, or hepatic or renal impairment. The absorption of some drugs can be affected by antacids and the renal excretion of certain pH dependent drugs may be altered. Lithium excretion may be increased. Local release of CO_2 after ingestion of

inappropriate amounts has been reported to cause abdominal discomfort or distension or in extreme cases, gastric damage.

2.4.1 OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

2.4.1.1 Justification for the application.

Sodium bicarbonate is widely used in dyspepsia both alone and as an ingredient in many indigestion remedies. Its mechanism of action is simple neutralisation of gastric acid. The present product is essentially similar to one such well established product. The application is made under Article 10 (1) of Directive 2001/83/EC. The active substance conforms to the Ph. Eur. Monograph for sodium bicarbonate. The formulation is a straightforward hard gelatin capsule containing sodium bicarbonate 500mg. All of the excipients have well-established pharmaceutical use. There are no claims in the Summary of Product Characteristics that are not known or inferred from the properties of the active substance.

2.4.1.2 Literature search strategy

The Pubmed and Toxline databases were the main sources of published data. Secondary use was made of scientific monographs and relevant publications by regulatory authorities.

2.4.1.3 Comment on the published data

"Well established use" presumes that there is a general recognition of efficacy and an acceptable level of safety. The use of sodium bicarbonate as an antacid is long established (more than a century). The mechanism of action in dyspepsia is simple. The physiological role of bicarbonate in acid-base regulation is recognized and information may be found in any standard textbook of biochemistry or physiology. There is little recent published investigational work on efficacy or safety and overall little documented toxicity. There are some published case histories of ingestion of inappropriate amounts. There is some reasonably recent published data on disposition and fate of bicarbonate.

Animal studies do not demonstrate any effects on genotoxicity, mutagenicity or reproduction and development. The TOXNET database of the National Library of Medicine contains a Hazardous Substances Data Bank (HSDB) monograph on sodium bicarbonate that forms a comprehensive review of its toxicology.

2.4.2 PHARMACOLOGY

The present product is a 500 mg capsule intended for use as an antacid in the treatment of dyspepsia. It may also be considered for use in the treatment of metabolic acidosis, not requiring parenteral therapy.

The antacid effect is a simple neutralization reaction in the stomach between sodium bicarbonate and hydrochloric acid and may be written as follows.

$$HCl + NaHCO_3 \rightarrow NaCl + CO_2 + H_2O$$

Excess bicarbonate ion is absorbed. CO_2 is produced in an aqueous environment and is relatively slowly released in the gas phase in the stomach (Fordtran et al, 1984). Much is also likely to be absorbed. The recommended doses are likely to produce only small amounts of gaseous CO_2. Absorbed bicarbonate ion enters the carbonic acid-bicarbonate ion buffer system as shown.

$$H^+ + HCO3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$

Excess bicarbonate ion pushes this equilibrium in the direction of metabolic alkalosis. Excess bicarbonate is normally cleared via renal elimination and carbon dioxide expiration.

2.4.3 PHARMACOKINETICS

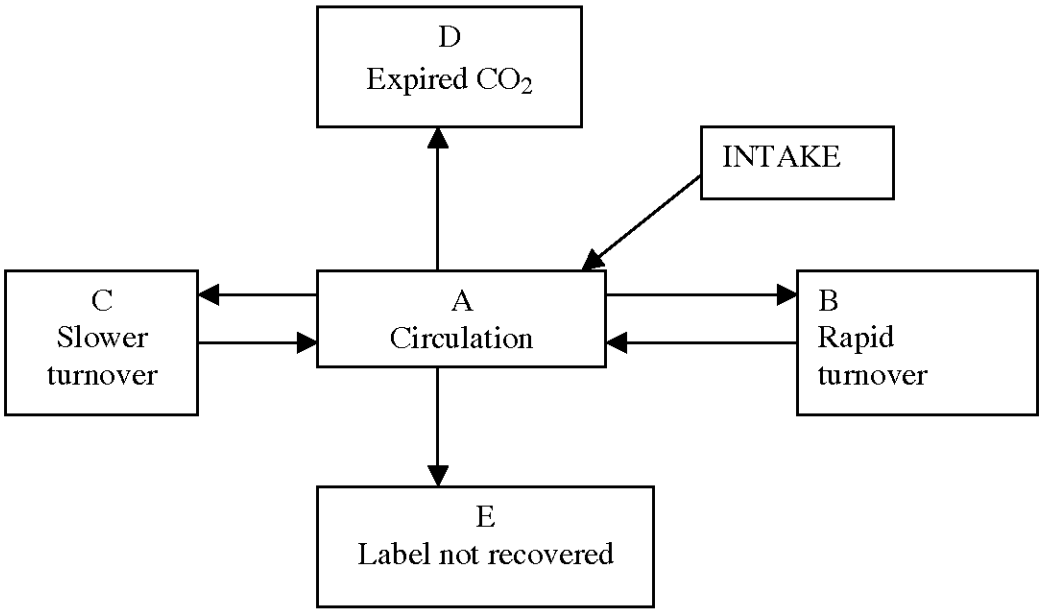
Bicarbonate is by definition a component of the carbonic acid-bicarbonate ion buffer system and not subject to conventional pharmacokinetic analysis. Studies with ^{13}C or ^{14}C labelled bicarbonate have permitted characterization of the fate of administered bicarbonate. A review by Leggett (2004) has been published from the point of view of characterization of the fate of ^{14}C ingested as bicarbonate. Several publications address the fate of ^{13}C labelled bicarbonate in humans.

Absorption

The sodium bicarbonate molecule is not systemically available. It rapidly reacts with hydrochloric acid to form sodium chloride, carbon dioxide and water as shown above in section 2.4.2. Excess bicarbonate ion is absorbed from the stomach and intestine. Carbon dioxide is formed in a liquid environment but rapid formation will result in gas production with possibly accompanying belching, reflux, flatulence, abdominal distension, gastric discomfort or in extreme cases, gastric damage. It is likely that only amounts in excess of the recommended dose will produce volumes of gas that will have potential for adverse effects (Fordtran et al, 1984). Dissolved carbon dioxide will be systemically absorbed but the literature is not clear on this. A number of studies however have compared the fate of intravenously and orally administered $NaH^{13}CO_2$ in humans, by measuring $^{13}CO_2$ elimination in breath. (Hoerr et al. 1989; Meineke et al. 1993). The recovery of $^{13}CO_2$ was similar for both intravenously and orally administered bicarbonate and points to bicarbonate being well absorbed. Sodium will also be absorbed. This will contribute to the body's sodium load. Each 500 mg capsule of sodium bicarbonate will contain 137 mg sodium or 274 mg sodium per gram sodium bicarbonate. This is a relatively small proportion of the adult daily intake so is only likely to be problematic in cases of excess or prolonged use or in people in whom extra sodium is contraindicated.

Distribution

Bicarbonate is a normal body constituent, present in the systemic circulation and exogenously administered material will enter the body pool. The distribution would be expected to reflect that of the body pool. There will be a dynamic exchange of ingested bicarbonate with the available pool and a slower exchange or sequestration of individual components with that in structural tissues, for example carbon with bone carbonate or with ureagenesis. Leggett (2004) characterizes this distribution as shown below, reflecting the fate of labelled carbon, noting that compartments B and C are sometimes merged.



Compartment B represents well perfused tissues, such as liver, heart and brain. Compartment C represents more slowly perfused tissues such as muscle, fat and skin. Compartment B represents mainly bone and losses by minor excretory pathways. Ram et al. (1999) carried out a distribution study in sheep following a one-hour infusion of $NaH^{13}CO_2$ or $NaH^{14}CO_2$. The largest concentrations of isotope at the end of the infusions were seen in the more metabolically active tissues; liver, jejunum, kidney, with

lower concentrations in fat and muscle. However the largest absolute amounts of label were seen in tissues of greatest mass, mainly muscle, fat and skin. Of the total label sequestered in sheep, more than 20% was reported to be in bone; however this was still less than 2% of the infused dose. This appears typical of other animal studies.

Elimination

Results from studies in animals and in humans are reasonably consistent. About 2% of a dose of labelled bicarbonate is excreted in urine and less than 0.5% is excreted in faeces (data reviewed by Leggett, 2004).

Overall view

Ingested bicarbonate enters the body pool of bicarbonate and is chiefly eliminated as expired carbon dioxide. Small amounts are eliminated by other routes, chiefly urine. Via exchange and sequestration, carbon will distribute widely in body tissues, especially bone. Administration of sodium bicarbonate will not change this homeostatic process, except in larger quantities to alter the direction of the carbonic acid-bicarbonate ion buffer system in the direction of metabolic alkalosis.

Drug interactions

Sodium bicarbonate has the potential to interact with other medications via two mechanisms.

(i) Effects on drug absorption

In general it is considered preferable not to take antacids with other drugs because of their capacity to impair absorption, often by complexation mechanisms. There are a large number of examples and the British National Formulary contains a list of these. Drugs for which absorption is reduced include ACE inhibitors, many antibacterials some

antimalarials, some antivirals, bisphosphonates, itraconazole, ketaconazole, penicillamine.

(ii) Effects on drug elimination

Sodium bicarbonate increases the elimination of lithium, resulting in lower plasma concentrations of lithium. The mechanism is not clear. An alkaline urine will increase the excretion of aspirin.

There is no recent published review of this area. Older reviews are those of Gugler and Allgayer (1990), Sadowski (1994) and Maton and Burton (1999).

2.4.4 TOXICOLOGY

Sodium bicarbonate is a very widely used agent, with long and traditional use as an antacid. Despite its wide use and as noted by Thomas and Stone (1994), little documented toxicity has occurred. Thomas and Stone document a case history and review the risks of acute and chronic ingestion pointing to metabolic alkalosis, hypernatremia, hypertension, gastric rupture, hyporeninemia, hypokalemia, hypochloremia, intravascular volume depletion, and urinary alkalinization. These all relate to the known properties of sodium bicarbonate. A more recent report of ingestion of large quantities of baking soda by a 68-year old man (Ajbani et al. 2007) reported the presence of a hyponatraemic, hypochloraemic, hypokalaemic, metabolic alkalosis. The estimated quantities ingested were not stated. The authors noted that daily doses of up to 140 g sodium bicarbonate daily have been tolerated with only a mild elevation in serum bicarbonate in healthy subjects (van Goidsenhoven et al, 1954).

Acute toxicity

The LD50 in rats has been variously estimated as 4.22 g/kg (Hazardous Substances Data Bank Monograph) and in the range of 7.6 g/kg to 8.9 g/kg (Anon, J Am Coll Toxicol). The Hazardous Substances Data Bank Monograph describes various studies with administration of 3 g/kg to 9 g/kg to rats. Clinical signs of toxicity included lethargy, ataxia, diarrhoea and hunched posture. Surviving animals had a normal appearance from day 2 following administration.

Chronic toxicity

There is limited published work. In a 2 year study, male rats received sodium bicarbonate as 0.64% of their diet. With the exception of a lower body weight there were no adverse findings (Hazardous Substances Data Bank Monograph).

Clinico-chemical and haematological findings

No published data.

Fertility, embryotoxicity, peri-postnatal toxicity

No published findings of developmental or reproductive toxicity (Hazardous Substances Data Bank Monograph).

Oncogenic/carcinogenic potential, mutagenicity

No published indications of genotoxicity or carcinogenic effects.

Immunotoxicity

No published evidence of any effects.

Impurities and excipients

The active substance and the excipients conform to the requirements of the Ph. Eur. and have well established pharmaceutical use.

2.4.5 INTEGRATED OVERVIEW AND CONCLUSIONS

Sodium bicarbonate is a very well known agent that has had long use as an antacid. Considering its widespread use over many decades, there have been few published reports of toxicity from its use. Bicarbonate is a normal body constituent, part of the physiological carbonic acid buffering system. Its use is associated with abdominal discomfort because of carbon dioxide release but only ingestion of large quantities is likely to produce damaging amounts. Bicarbonate is well absorbed and excessive amounts or predisposing conditions could produce a metabolic alkalosis. Relatively large amounts are well tolerated in normal people and the LD50 in animals is high. The contraindications and precautions are well recognized. The amount of sodium ingested at normal doses is small relative to the daily intake in the otherwise healthy person (137 mg per 500 mg capsule) but will nevertheless be contraindicated in persons requiring restricted salt intake. Toxicological studies in animals have not demonstrated any genotoxic, carcinogenic or reproductive toxicity effects. The present product is administered at relatively low doses, consistent with currently recommended doses of the reference product. The Summary of Product Characteristics is similar to that already approved for the reference product and is appropriate for the substance.

2.4.6 LIST OF LITERATURE CITATIONS

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Meineke I, De Mey C, Eggers R, Bauer FE. Evaluation of the 13CO2 kinetics in humans after oral application of sodium bicarbonate as a model for breath testing. Eur J Clin Invest. 1993 Feb;23(2):91-6.

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Sadowski DC. Drug interactions with antacids. Mechanisms and clinical significance.Drug Saf. 1994 Dec;11(6):395-407.

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Van Goidsenhoven GM, Gray OV, Price AV, Sanderson PH. The effect of prolonged administration of large doses of sodium bicarbonate in man. Clin Sci (Lond). 1954 Aug;13(3):383-401.

1.4.2 Non-Clinical

According to his/her respective qualifications the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I, Part I 1.4 of Directive 2001/83/EEC, as amended.

Name of the expert: [redacted] Signature: [redacted]

Address: [redacted]

Date: [redacted]

Relationship to the Company:

The expert has no relationship with the company other than acting as a consultant in the preparation of this report.

According to Annex I of Directive 2001/83/EEC as amended, brief information (*curriculum vitae*) on the educational background, training and occupational experience is attached overleaf.

INFORMATION ABOUT THE EXPERT