New Medicine Assessment

NEPHROTRANS (SODIUM HYDROGEN CARBONATE GR)

Recommendation: BLACK for the following indications:

For the treatment of metabolic acidosis and for maintenance treatment against recurrence of metabolic acidosis in adults with chronic renal impairment.

Summary of supporting evidence:

- There is an absence of evidence comparing the efficacy and tolerability of Nephrotrans to standard sodium bicarbonate formulations.
- Numerous variables can affect the stability and functionality of enteric coatings.
- Most of the common side effects of sodium bicarbonate are caused by CO_2 released through a reaction in the stomach, and include belching, gastric distension, and flatulence.
- Nephrotrans capsules are more than double the cost of standard capsules. Cost per capsule is low, but when considering a dose of 6-10 capsules daily for an undefined course length, the cost impact becomes relevant.

Details of Review

Name of medicine (generic & brand name)**:**

Sodium bicarbonate (Nephrotrans)

Strength(s) and form(s):

500mg gastro-resistant capsules, soft

Dose and administration:[1]

The dosage depends on the severity of metabolic acidosis, based on the results of blood gas analysis or determination of serum bicarbonate.

The mean dosage is 3 to 5 g sodium hydrogen carbonate per day, equivalent to 40-65 mg sodium hydrogen carbonate per kg body weight per day.

The daily dose can be achieved by taking 6 to 10 capsules of Nephrotrans 500 mg.

To be swallowed whole throughout the day with sufficient liquid.

BNF therapeutic class / mode of action:

Fluids and electrolytes.

Sodium hydrogen carbonate is a salt whose essential pharmacological properties result from its physiological role as a component of the HCO_3/CO_2 buffer. Sodium hydrogen carbonate leads to an increase in the body's pH level.[1]

Licensed indication(s):

For the treatment of metabolic acidosis and for maintenance treatment against recurrence of metabolic acidosis in adults with chronic renal impairment.

Proposed use (if different from, or in addition to, licensed indication above):

As per licensing

Course and cost:

3–5 g daily in divided doses, adjusted according to response.

The daily dose can be achieved by taking 6 to 10 capsules of Nephrotrans 500 mg.

Sodium bicarbonate 500mg GR capsules £18.75 for 100 capsules

£1.12 - £1.87 /day

Prices as per drug tariff Dec 2022

Current standard of care/comparator therapies:

Sodium bicarbonate is given by mouth for chronic acidotic states such as uraemic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For severe metabolic acidosis, sodium bicarbonate can be given intravenously.[2]

Relevant NICE guidance:

NG203 Chronic kidney disease: assessment and management

Oral bicarbonate supplements in the management of metabolic acidosis

Detailed advice on the management of metabolic acidosis is beyond the scope of this guideline. If uncertain, seek advice from your local renal service.

1.12.8 Consider oral sodium bicarbonate supplementation for adults with both:

- a GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5) and
- a serum bicarbonate concentration of less than 20 mmol/litre.

Background and context

Overt chronic metabolic acidosis in CKD patients develops after a drop in glomerular filtration rate (GFR) to less than approximately 25 mL/min/1.73 m^2. The pathogenic mechanism seems to be a lack of tubular bicarbonate production, which in healthy individuals neutralizes the acid net production.[3]

The oral administration of sodium bicarbonate is a pharmaceutical technological challenge: firstly, the drug must not be released in the stomach as the acidic gastric juice would immediately transform bicarbonate into carbon dioxide. The desired therapeutic effect would not be achieved and the produced gas could cause abdominal pain and flatulence. Secondly, sodium bicarbonate should be rapidly released from the solid dosage form into the intestinal fluid as residuals of bicarbonate in ileum and colon may cause diarrhoea and flatulence. Both criteria can be fulfilled by enteric-coated dosage forms of sodium bicarbonate. It is well known from the literature that numerous variables can affect the stability and functionality of enteric coatings. External factors, such as mechanical forces, pH values and temperature, as well as inter-formulational interactions with external substances like buffer substances or macrogol, may influence the drug release. Intra-formulational interactions (e.g. with solvents, plasticizers or core material) also influence the dissolution pattern. In sodium bicarbonate formulations the permeability of hydrogen ions has an extraordinary impact as traces of protons in the core could initiate gas forming and consequently cause film rupturing. Dose dumping would result.[4]

Summary of evidence

Summary of efficacy data in proposed use:

Derbyshire Medicines Management, Prescribing and Guidelines Derbyshire Primary Care Formulary[5]
Chapter 9: NUTRITION AND BLOOD Updated: July 2022

9.2.1.3 Oral bicarbonate Sodium bicarbonate capsules is Green consultant/ specialist recommendation. Sodium bicarbonate gastro-resistant capsules (Nephrotrans) is RED- reserved for patients who cannot tolerate other sodium bicarbonate preparations due to gastric side effect.

Summary of safety data:

Łoniewski et al (2014)[6]

In clinical studies to date, NaHCO3 has had few notable side effects when given to CKD patients. Most of the common side effects were caused by CO_2 released through a reaction in the stomach, and included belching, gastric distension, and flatulence. Practitioners must be aware that higher alkali doses might cause fluid retention and worse blood pressure control in patients treated with very low GFR.

Short-term and long-term studies also show that $NaHCO_3$ therapy can reduce serum potassium, an outcome that can be beneficial in CKD patients who are at increased risk of hyperkalemia, particularly in the later stages of CKD and in such patients taking angiotensin-converting enzyme inhibitors.

Summary of Product Characteristics[1]

Contraindications
- Hypersensitivity to the active substance, soya, peanuts, or to any of the excipients

- metabolic alkalosis

- hypokalaemia

- hypernatraemia

- low sodium diet

Special warnings and precautions for use

The effect of Nephrotrans 500 mg should initially be monitored at intervals of at least one to two weeks (e.g. by pH measurement, standard bicarbonate, alkali reserve), especially at higher doses. Plasma electrolytes, especially sodium, potassium and calcium, should likewise be regularly monitored. These checks should also be performed regularly during long-term medication. Further dosing should be determined based on

the outcome of these checks. Any possible hyperalkalinity can be corrected by a dose reduction.

Particular caution is required in the presence of hypoventilation, hypocalcaemia and hyperosmolar conditions.

This medicinal product contains 137 mg sodium per capsule, equivalent to approximately 7% of the WHO recommended maximum daily intake of 2 g sodium for an adult. The maximum daily dose of this product (10 capsules) is equivalent to 68% of the WHO recommended maximum daily intake for sodium. This should be particularly taken into account for those on a low salt diet.

Nephrotrans 500 mg contains 50 mg sorbitol in each capsule. Patients with rare hereditary problems of fructose intolerance (HFI) should not take this medicinal product.

Interaction with other medicinal products and other forms of interaction
Due to the increase in pH levels in the stomach and intestines, absorption and excretion of weak acids and bases may be affected. This applies, for example, to sympathomimetics, anticholinergics, tricyclic antidepressants, barbiturates, H_2 antagonists, captopril and quinidine.

Functional interactions are possible with glucocorticoids and mineralocorticoids, androgens and potassium-depleting diuretics.

Vigilance is required for a possible effect on the solubility of medicines eliminated with the urine (e.g. ciprofloxacin).

Undesirable effects
Gastrointestinal disorders *Frequency Not known*: flatulence and abdominal pain.

Renal and urinary disorders *Frequency Not known*: promotion of calcium or magnesium phosphate nephrolithiasis in chronic use.

Musculoskeletal and connective tissue disorders *Frequency Not known*: hypocalcaemic tetany (muscle hyperexcitability due to decreased calcium) if the dose is exceeded. In patients with pre-existing disorders of the gastrointestinal tract, e.g. diarrhoea, exacerbation of such disorders is possible.

Skin and subcutaneous tissue disorders *Very rare*: allergic reactions due to soya oil.

Strengths and limitations of the evidence:

Comparative evidence to standard oral sodium bicarbonate formulations is absent.

Theoretical implication that enteric coated capsules may be better tolerated.

Summary of evidence on cost effectiveness:

None identified

Prescribing and risk management issues:

None identified

Commissioning considerations:

Innovation, need and equity implications of the intervention:

None identified

Financial implications of the intervention:

3–5 g daily in divided doses, adjusted according to response.

The daily dose can be achieved by taking 6 to 10 capsules of Nephrotrans 500 mg.

Sodium bicarbonate 500mg GR capsules £18.75 for 100 capsules = 19p/capsule

Sodium bicarbonate 500mg capsules £4.53 for 56 capsules = 8p/capsule

Sodium bicarbonate 600mg tablets £26.79 for 100 tablets = 27p/tablet

Standard capsules: £0.48 – £0.80/day = £14.40 – £24 /month

GR capsules: £1.14 – £1.90/day = £34.20 - £57 /month

Prices as per drug tariff Dec 2022

Service Impact Issues Identified:

None identified

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** recommends sodium bicarbonate 500mg oral capsules, RAG rated GREEN. No reference to GR capsules or the Nephrotrans brand.

The **Greater Manchester Medicines Management Group** (GMMMG) makes no reference to sodium bicarbonate in its formulary.

Legal Issues Identified:

None identified

Media/ Public Interest:

None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Nephrotrans 500mg gastro-resistant capsules", Stanningley Pharma Limited, June 2021. Available: https://www.medicines.org.uk/emc/product/12715

[2] British National Formulary, “Fluids and electrolytes” [Online]. Available: https://bnf.nice.org.uk/treatment-summaries/fluids-and-electrolytes/ [Accessed December 2022]

[3] Gaggl M et al, “Effect of oral sodium bicarbonate supplementation on progression of chronic kidney disease in patients with chronic metabolic acidosis: study protocol for a randomized controlled trial (SoBic-Study)”, *Trials*, vol. 14 (196)

[4] Breitkreutz J et al, “Enteric-coated solid dosage forms containing sodium bicarbonate as a drug substance: an exception from the rule?”, *Journal of Pharmacy and Pharmacology*, vol 59, pp 59–65, 2007

[5] Derbyshire Medicines Management, Prescribing and Guidelines Derbyshire Primary Care Formulary, “Chapter 9: NUTRITION AND BLOOD”, 2022. Available: http://www.derbyshiremedicinesmanagement.nhs.uk/assets/Clinical_Guidelines/Formulary_by_BNF_chapter_prescribing_guidelines/BNF_chapter_9/Chapter_9_nutrition_and_blood.pdf

[6] Łoniewski I et al, “Bicarbonate therapy for prevention of chronic kidney disease progression”, *Kidney International*, vol. 85, pp 529–535, 2014