SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sibnayal 8 mEq prolonged-release granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 282 mg of potassium citrate and 527 mg of potassium hydrogen carbonate. This corresponds to 7.9 mEq of alkali (i.e. 2.6 mEq of citrate and 5.3 mEq of hydrogen carbonate) and to 7.9 mEq of potassium (i.e. 308 mg of potassium).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release granules.

Green (potassium citrate) and white (potassium hydrogen carbonate), biconvex, 2 mm diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sibnayal is indicated for the treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged one year and older.

4.2 Posology and method of administration

Posology

Dosing is based on age and weight.
When initiating alkalising therapy, the target starting daily dose indicated below for each age group should be used and incrementally titrated to obtain the optimal dose that provides adequate metabolic acidosis control based on plasma bicarbonate levels.

- Adults: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 0.5 mEq/kg/day to optimal dose
- Adolescents from 12 years: initiation at 1 mEq/kg/day, with a maximal incremental increase/decrease of 1.0 mEq/kg/day to optimal dose
- Children from 4 to 11 year inclusive: initiation at 2 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose
- Children from 1 to 3 years inclusive: initiation at 4 mEq/kg/day, with a maximal incremental increase/decrease of 1.5 mEq/kg/day to optimal dose

When switching from another alkalising therapy to Sibnayal, treatment should be initiated at the target dose used with the previous therapy (in mEq/kg/day) and titrated where necessary as described above.

The maximum dose, regardless of the age group, is either 10mEq/kg/day or a total daily dose of 336 mEq, whichever is lower.

The total daily dose should be administered in two intakes. For each individual patient, the nearest dose to the target dose should be fixed by combining whole sachets of the two available strengths.

In case of vomiting within two hours after intake, the patient should take another dose. The use of this medicine requires medical supervision.

Special populations

Elderly
No dose adjustment is required.

Renal impairment
Sibnayal should only be used in individuals with glomerular filtration rate (GFR) > 44mL/min/1.73m². For individuals with GFR between 45 and 59 mL/min/1.73m² Sibnayal should only be used if the potential benefits are considered to outweigh the potential risks. See Table 1.

Table 1: Dosing recommendations in individuals with renal impairment

GFR mL/min/1.73m²	**Treatment of dRTA**
45-59	• Plasma potassium levels in the normal ranges: A regular monitoring of renal function parameters and blood potassium levels is necessary at starting dose and after new dose increase or if any decrease of GFR. Then frequency is according to physicians´s criteria, but at least twice a year (see section 4.4).

	• Elevated plasma potassium: Contraindicated
≤ 44	Contraindicated

Hepatic impairment
There is no need for specific target starting daily dose adjustment in patients with hepatic impairment.

Paediatric population
The safety and efficacy of Sibnayal in children below one year of age have not been established. No data are available.

Method of administration

For oral use.

The total daily dose is administered twice daily, typically twelve hours apart.

Sibnayal must be taken orally, swallowed with a large glass of water.
The full dose of granules per intake can be swallowed in several smaller portions if necessary, but the content of each sachet must be entirely taken.
Doses should be taken preferably during meals.

For patients who are unable to swallow granules as described above, the granules may be mixed (without crushing) with small amounts of soft food (e.g., fruit puree, yoghurt). The Sibnayal soft food mixture must be used immediately and cannot be stored. The mixture should be swallowed without chewing. Care should be taken to ensure that Sibnayal is not retained in the mouth.

In no instance granules must be mixed with hot food, hot liquid or alcohol or chewed or crushed as this can disrupt their prolonged release properties and may lead to large sudden release of alkalising agent that could affect product efficacy and safety (see section 5.2).

Sibnayal granules are not suitable for administration via feeding tubes due to high risk of obstructing the tubes.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Renal impairment with GFR ≤ 44 mL/min/1.73m².

Hyperkalaemia.

4.4 Special warnings and precautions for use

Hyperkalaemia and cardiotoxicity

Sibnayal should be used with caution in patients who have conditions pre-disposing them to hyperkalaemia, such as renal impairment, or crush syndrome, as a further rise in plasma potassium may lead to cardiac arrest. Close monitoring of plasma potassium in patients at risk is required at starting dose and after new dose increase or in case of worsening of pre-existing disease. Then frequency is according to physicians´s criteria, but at least twice a year.

Sibnayal should be used with caution in case of combination with other products increasing plasma potassium or predisposing to cardiac dysrhythmia (see section 4.5).

Gastrointestinal disorders

Sibnayal should be used with caution in patients having gastro-intestinal disorders as they could affect efficacy and safety, such as malabsorption, delayed gastric emptying, diarrhoea, nausea, vomiting. In such cases the blood bicarbonate levels should be regularly monitored and dose adjusted to maintain within normal ranges.

The matrix of the granules can be found in the stools, which does not affect the efficacy or safety of Sibnayal.

Renal insufficiency

Sibnayal should only be used in individuals with glomerular filtration rate (GFR) > 44mL/min/1.73m². For individuals with GFR between 45 and 59 mL/min/1.73m² Sibnayal should only be used if the potential benefits are considered to outweigh the potential risks. For these patients doses should be adjusted by regular monitoring of plasma bicarbonate and potassium (see section 4.2). Special care should be taken in elderly people in whom renal function can be decreased.

Potassium contents

Sibnayal 8 mEq contains 308 mg of potassium per sachet. This is to be taken into consideration if the patient has a reduced kidney function or if the patient is on a controlled potassium diet.

Sibnayal 24 mEq contains 924 mg of potassium per sachet. This is to be taken into consideration if the patient has a reduced kidney function or if the patient is on a controlled potassium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Medicinal products that may increase plasma potassium or induce hyperkalaemia

Concomitant use of Sibnayal with medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, ciclosporin or other medicinal products such as heparin sodium or nonsteroidal anti-inflammatory medicinal products) necessitates monitoring of potassium plasma levels (see section 4.4).

Medicinal products affected by plasma potassium disturbances

Periodic monitoring of plasma potassium and ECG is recommended when Sibnayal is administered with medicinal products affected by plasma potassium disturbances due to the potential risk for a proarrhythmic effect (e.g. digitalis glycosides, corticosteroids, anti-arrhythmics such as quinidine, amiodarone, chlorpromazine, cisapride or sparfloxacine).

Medicinal products affected by increased urine pH

Patients with dRTA have alkaline urine due to their proton secretion defect. This may impact the excretion of medications into the urine (such as an increase of the elimination of salicylates, tetracyclines, and barbiturates and a decrease in the elimination of quinidine) or reduce the effectiveness of methenamine. As Sibnayal may further increase urine pH to a small extent, the interaction of alkaline urine with these medications may be enhanced.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Sibnayal in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy,

embryonal/foetal development, parturition or postnatal development (see section 5.3).
Sibnayal should only be used during pregnancy if the expected benefits outweigh the potential risks. Although during pregnancy and more so during labour, there is more risk associated to a potentially severe acidosis and hypokalaemia in dRTA patients than to alkali treatment, in women with problem pregnancies there might be an increased risk to develop hyperkalemia when potassium intake is high.

Breast-feeding

Potassium is excreted in human milk, but at therapeutic doses of Sibnayal no effects on the breastfed newborns/infants are anticipated.
Sibnayal can be used during breast-feeding.

Fertility

Potassium citrate and potassium hydrogen carbonate are not known to affect fertility.

4.7 Effects on ability to drive and use machines

Sibnayal has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are abdominal pain (7 patients, 14%, very common), upper abdominal pain (in 4 patients, 8%, common) and gastro-intestinal pain (in 1 patient, 2%, common).
Nausea (in 1 patient, 2%, common) can be experienced at initiation of therapy.

Tabulated list of adverse reactions

The list of adverse reactions is based on the experience with Sibnayal in clinical trials.
The frequency of adverse reactions is defined using the following convention: very common (1/10) ; common (1/100 to <1/10) ; uncommon (1/1000 to <1/100) ; rare (1/10000 to <1/1000) and very rare (<1/10000).

Gastrointestinal disorders:

- abdominal pain as very common
- abdominal pain upper, diarrhoea, dyspepsia, gastrointestinal disorder, gastrointestinal pain, nausea and vomiting as common.

Description of selected adverse reactions

Gastrointestinal disorders
Gastro-intestinal pain, abdominal pain and upper abdominal pain were generally of mild or moderate intensity and resolved within 24 hours without the need to modify or stop the treatment. All other gastrointestinal adverse reactions (dyspepsia, vomiting, diarrhoea) were also of mild or moderate intensity, and resolved within 1 to 3 days, without modification or interruption of treatment.

Paediatric population

In clinical trials, although numbers were small, the safety profile was comparable for adults and children.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Reports of a laxative effect after excessive oral doses of individual alkalising salts have occurred. An acute massive intake of potassium can cause hyperkalaemia resulting in nausea, vomiting, and diarrhoea and in severe cases paraesthesia, muscular weakness, mental confusion, electrocardiographic abnormalities (large and symmetric T waves), arrhythmia, atrioventricular block and heart failure.
Hyperkalaemia is a particular concern in patients with underlying renal insufficiency.
In case of severe hyperkalaemia, patients should be monitored (mostly plasma potassium level and ECG) and the appropriate symptomatic and supportive therapy instituted in specialised care units, where emergency treatments leading to rapid elimination of potassium such as ion exchange resin, combination of insulin-dextrose or β2 mimetics (salbutamol) or haemodialysis will be implemented.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: mineral supplements, potassium, ATC code: A12BA30.

Mechanism of action

Sibnayal is a fixed-dose combination of potassium citrate and potassium hydrogen carbonate (also known as potassium bicarbonate) as prolonged release granules.

The pharmacological properties of Sibnayal are directly linked to the capacity of potassium citrate and potassium hydrogen carbonate to maintain electrolyte balance. Both act as alkalising agents and buffer the metabolic acidosis. Sibnayal provides a source of potassium to correct hypokalaemia. In addition, citrate acts also as a calcium chelating agent.

Pharmacodynamic effects

In a randomised, double blind, placebo-controlled, two-period, incomplete crossover study in healthy adults, Sibnayal at doses ranging from 1.0 to 2.9 mEq/kg/day during 5 days was shown to increase urine pH (marker of alkalinising effect in healthy subjects) with a dose-proportional effect as compared to placebo. The effect was maintained over 12 hours at all the doses evaluated.

Clinical efficacy and safety

The efficacy and safety of Sibnayal for the treatment of dRTA was evaluated in a multi-centre, openlabel, sequential study that included 37 patients with an established diagnosis of dRTA (7 adults, 10 adolescents (12 – 17 years), 15 children (4 – 11 years), 5 infants (1- 4 years)) who were being treated with their standard-of-care (SoC) short-acting alkalising agents in repeated daily intakes . Patients continued on their SoC for 5 days (n=35) and then received Sibnayal twice daily, initially during a titration period to establish the optimal dose (up to 30 days duration) and then for 5 days at this optimal dose (n=32).

With Sibnayal, the primary endpoint showed that the mean (SD) plasma bicarbonate pre-dose levels during 3 days of treatment at steady state were 23.1 (1.62) mmol/L with 90% (26/29) of the patients achieving 3-day mean normal bicarbonate levels. All age groups were well controlled (adults: 23.8 mmol/L, adolescents: 23.3 mmol/L, children: 22.7 mmol/L and infants: 21.8 mmol/L). Plasma potassium levels were also well controlled, with a mean (SD) of 4.0 (0.44) mmol/L; 83% (24/29) of the patients at normal levels.

Most patients (93%, 28/30) had the urine calcium/creatinine ratio in the normal ranges, 41% (7/17) had the urine citrate/creatinine in the normal ranges and 55% (11/20) had the urine calcium/citrate ratio in the normal ranges.
Most patients (61.3%, 19/31) found an improved palatability with the change of treatment.
During 24 months of therapy, all the effects were generally maintained, although some variability was observed in the values of the metabolic parameters and responder rates. At least 80% of the patients presenting a compliance level of or above 75% overtime. Health-related quality of life of the patients was improved and maintained high (above 80%) throughout the study.

With SoC the mean (SD) plasma bicarbonate pre-dose levels during 3 days of treatment at steady state was 21.7 (3.06) mmol/L with 45% (13/29) of the patients achieving 3-day mean normal bicarbonate levels. Only adults (24.1 mmol/L) were well controlled and adolescents (21.6 mmol/L), children (19.9 mmol/L) and infants (19.9 mmol/L) were below normal range.
Plasma potassium levels were also well controlled, with a mean (SD) of 3.8 (0.44) mmol/L; 83% (24/29) of the patients at normal levels.
Most patients (93%, 28/30) had the urine calcium/creatinine ratio in the normal ranges, only 6% (1/17) had the urine citrate/creatinine in the normal ranges and 15% (3/20) had the urine calcium/citrate ratio in the normal ranges.

5.2 Pharmacokinetic properties

Sibnayal is a prolonged-release granules formulation to cover a 12-hour treatment period after administration.
Pharmacokinetic features of citrate, bicarbonate and potassium are based on the literature.

Absorption

Oral citrate is absorbed at a pH between 4.8 and 6.4 along the upper portion of the small intestine (duodenum, early part of jejunum). Under these conditions, the intestinal absorption of citrate is rapid and almost complete.

Oral bicarbonate is absorbed throughout the gastrointestinal tract. Bicarbonate neutralises gastric acid with the production of CO_2 eliminated by the respiratory route. Bicarbonate not involved in that reaction is rapidly absorbed by the intestinal mucosa.

The potassium ions are fully absorbed, irrespective of the amount consumed. The majority of potassium absorption occurs in the small intestine, mainly through passive diffusion.

Distribution and biotransformation

Most of the citrate in the blood circulates unbound and the remaining quota is complexed to calcium, potassium or sodium. The citrate ion from oral alkali citrates undergoes oxidative metabolic breakdown to carbon dioxide (CO_2) or bicarbonate. Consequently, a basifying effect is associated with its metabolism. Ingestion of 36 mmol of citrate (i.e. 108 mEq) is equivalent to less than 2% of the daily turnover of citrate involved in energy metabolism within the body.

The absorbed bicarbonate is distributed like the endogenous bicarbonate in the intracellular and extracellular compartments of the organism. Bicarbonate is not really metabolised. However, bicarbonate is in equilibrium with hydrogen ions and carbon dioxide and, though its concentration, regulates the acid-base balance.

Potassium is carried from extracellular fluids to the intracellular fluids, and its distribution between cells is tightly controlled, with only 1.5–2.5% of total body potassium found in the extracellular fluid. A large proportion of the body burden of potassium (98%) is found in muscle and the skeleton, and it is also present in high concentrations in the blood, central nervous system, intestine, liver, lung and skin. An active ion transport system maintains the gradient across the plasma membrane.

Elimination

Citrate is mainly eliminated by the renal route. In its trivalent form, it is filtered freely through the renal glomerulus. Dietary alkali absorption increases citrate excretion by inhibiting its reabsorption at the mitochondrial level and by increasing its secretion by the nephron.
Bicarbonate provides an alkali load and therefore stimulates an increase in urinary excretion of citrate. Increased excretion of bicarbonate in the urine also occurs. Bicarbonate can also be partially eliminated by the respiratory route (in the form of CO_2). The major excretory route of potassium is via the kidneys (90%). The rest is eliminated in the faeces and small amounts may also be excreted in sweat.

Special population

Pharmacokinetics of potassium can be modified in patients with renal impairment for whom glomerular filtration of potassium is less active, in cardiac patients who present a susceptibility to hyperkalaemia and in adrenocortical patients for whom the risk of hyperkalaemia is accentuated.
Pharmacokinetics of citrate, bicarbonate and/or potassium can be modified in patients with gastrointestinal issues (e.g. malabsorption, delayed gastric emptying, oesophageal compression, intestinal obstruction or other chronic gastro-intestinal disease) that could modify absorption.
Pharmacokinetics should not be modified in patients with hepatic impairment, or in patients with overweight or obesity.

Interaction with alcohol

When Sibnayal is mixed with alcohol *in vitro*, the rate of dissolution of the granules increases and can occur rapidly leading to a loss of the prolonged-effect (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveals no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core granules

Hypromellose (E464)
Microcrystalline cellulose (E460(i))
Glycerol dibehenate
Magnesium stearate (E470b)
Silica colloidal anhydrous
Magnesium oxide, heavy (E530)

Coating

Ethylcellulose (E462)
Chlorophyllin (E140 (ii))

Technological agent

Talc (on coated granules)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Three-layered foil (polyethylene terephthalate polyester/aluminium/low density polyethylene) sealed sachet for single use.

Packs of 60 sachets.
Multipacks containing 120 (2 packs of 60) sachets.
Multipacks containing 180 (3 packs of 60) sachets.
Multipacks containing 240 (4 packs of 60) sachets.
Multipacks containing 300 (5 packs of 60) sachets.
Multipacks containing 360 (6 packs of 60) sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After opening the sachet, discard any unused content.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

ADVICENNE
262 rue du Faubourg Saint Honoré, 75008 Paris, France

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 46766/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2021

10 DATE OF REVISION OF THE TEXT

27/09/2023