1 Ringers (solution for infusion)

Ringers solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients

The ingredients in **Ringers** solution for infusion comprise:

- sodium chloride (8.6g/L),
- potassium chloride (0.3g/L) and
- calcium chloride dihydrate (0.33g/L) in Water for Injections.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Ringers is a clear colourless solution, for intravenous infusion.

Ringers infusion solution is sterile and non-pyrogenic. There is no antimicrobial agent or buffer added. It is an isotonic intravenous solution with pH 5.0 – 7.5 and an osmolality of 308mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ringers solution for infusion is indicated for restoring the loss of water and electrolytes as required by the clinical condition of the patient.

4.2 Dose and method of administration

Ringers solution for infusion is for intravenous infusion, as directed by the physician. The dosage, volume, rate and duration of administration of **Ringers** solution for infusion is dependent upon the age, weight, clinical conditions of the patient and concomitant therapy, and administration should be determined by a physician experienced in intravenous fluid therapy.

Fluid balance and plasma electrolyte concentrations (sodium, potassium, calcium and chlorides) must be monitored during administration.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Do not administer unless the solution is clear and seal is intact. Only sterile and nonpyrogenic equipment must be used for intravenous administration. As with all parenteral solutions, compatibility of the additives with the solution must be assessed before addition.

Before adding a substance or medication, verify that it is soluble and/or stable in **Ringers** solution for infusion and that the pH range of **Ringers** solution for infusion is appropriate. The instructions for use of the medication to be added and other relevant literature must be consulted. Those additives known or determined to be incompatible should not be used. Consult with a pharmacist, if available. If in the informed judgment of the physician, it is deemed advisable to introduce additives, use aseptic technique. After addition, if there is discoloration, colour change and/or the appearance of precipitates, insoluble complexes or crystals, do not use. Mix thoroughly when additives have been introduced. Refer to instructions below. Solutions containing additives should be used immediately, and not stored. Do not reconnect any partially used containers.

The product should be used for one patient on one occasion only. Any unused portion should be discarded.

Directions for use of Viaflex plastic container

Do not connect flexible plastic container in series in order to avoid air embolism due to possible residual air contained in the primary container. Vented intravenous administration sets with the vent in open position, or pressurising intravenous solutions contained in flexible plastic containers to increase flow rate can also result in air embolism if the residual air in the container is not fully evacuated prior to administration. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

To open

Tear over wrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilisation process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired. If supplemental medication is desired, follow directions below.

Preparation for administration

Ringers solution for infusion is a sterile preparation. Thus aseptic technique must be applied throughout administration.

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at the bottom of container.
3. Attach administration set.

To add medication

Warning: Additives may be incompatible (see sections 4.4, 4.5 and 6.2).

To add medication before solution administration

Prepare medication site. Using syringe with 19 to 22-gauge needle, puncture resealable medication port and inject. Mix solution and medication thoroughly. For high-density medication, such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

To add medication during solution administration

Close clamp on the set. Prepare medication site. Using syringe with 19 to 22-gauge needle, puncture resealable medication port and inject. Remove container from IV pole and/or turn to upright position. Evaluate both ports by squeezing them while container is in the upright position. Mix solution and medication thoroughly. Return container to in-use position, re-open the clamp and continue administration.

4.3 Contraindications

Ringers solution for infusion is contraindicated in patients with:

- known hypersensitivity to the product or any ingredients in the formulation,
- extracellular hyperhydration or hypervolaemia,
- hypertonic dehydration,
- hyperkalaemia,
- hypernatraemia,
- hypercalcaemia,
- hyperchloraemia,
- severe renal insufficiency (with oliguria/anuria),
- uncompensated cardiac failure,

- severe hypertension,
- general oedema and ascitic cirrhosis,
- concomitant digitalis therapy.

As for other calcium-containing infusion solutions, concomitant treatment with ceftriaxone and Ringers solution for infusion is contraindicated in newborns (≤ 28 days of age), even if separate infusion lines are used (risk of fatal ceftriaxone calcium salt precipitation in the neonate's bloodstream). In patients, older than 28 days (including adults), Ringers solution for infusion must not be administered simultaneously with ceftriaxone through the same infusion line (see section 4.5).

4.4 Special warnings and precautions for use

Monitoring of serum sodium is particularly important for hypotonic fluids. Ringers solution for infusion has an osmolality of 308mOsm/kg.

High volume infusion must be used under specific monitoring in patients with cardiac or pulmonary failure and in patients with non-osmotic vasopressin release (including SIADH), due to the risk of hospital-acquired hyponatraemia.

Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (brain oedema) characterised by headache, nausea, seizures, lethargy and vomiting. Patients with brain oedema are at particular risk of severe, irreversible and life-threatening brain injury.

During long-term parenteral treatment, a convenient nutritive supply must be given to the patient.

Solutions containing potassium salts (including Ringers solution for infusion) should be administered with caution to patients with cardiac disorders, or conditions predisposing to hyperkalaemia such as:

- renal impairment or adrenocortical insufficiency,
- acute dehydration, or extensive tissue injury or burns,
- see also section 4.5.

Depending on the volume and rate of infusion, intravenous administration of Ringers solution for infusion can cause:

- fluid and/or solute overload resulting in overhydration and, for example, congested states, including pulmonary congestion and oedema,
- clinically relevant electrolyte disturbances and acid-base imbalance.

Ringers solution for infusion should be administered with particular caution to patients with hypertension, heart failure, fluid overload, peripheral or pulmonary oedema, impaired renal function, pre-eclampsia, aldosteronism or other conditions or treatment (e.g. corticoids/steroids) associated with sodium retention (see section 4.5).

Clinical evaluation and periodic laboratory determinations may be necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient or the rate of administration warrants such evaluation.

Solutions containing calcium salts should be used with caution in patients with hypercalcaemia or conditions predisposing to hypercalcaemia, calcium renal calculi or a history of such calculi.

Because of the presence of calcium:

- care should be taken to prevent extravasation during intravenous infusion,
- the solution should be given cautiously to patients with impaired renal function or diseases associated with elevated vitamin D concentrations such as sarcoidosis,

- due to the risk of coagulation precipitated by its calcium content, Ringers solution for infusion must not be added to or administered simultaneously through the same tubing with citrate anticoagulated/preserved blood.

Ringers solution for infusion contains insufficient concentrations of potassium and calcium to be used for maintenance of these ions or to correct their deficits. Hence, after dehydration is treated, the IV fluid has to be changed to a maintenance fluid that will provide these ions.

Ringers solution for infusion should be used with caution in patients at risk of hyperchloraemia. Administration of Ringers solution for infusion may result in acute kidney injury (AKI). Plasma chloride levels and renal function should be closely monitored.

Use in renal impairment
Ringers solution for infusion should be administered with particular caution, to patients at risk of severe renal impairment. In such patients, administration of Ringers solution for infusion may result in electrolyte abnormalities.

Use in the elderly
The volume/rate/dose of infusion for an elderly patient should be cautious, usually starting at the low end of the dosing range, considering that elderly patients are generally more likely to have hepatic, renal, cardiac, and/or other disease, and/or other concomitant medicinal therapy.

Paediatric use
The use of Ringers solution for infusion in paediatric patients should be based on clinical practice.

Children (including neonates and older children) are at risk of developing hyponatraemia as well as for developing hyponatraemic encelophathy. The infusion of low sodium fluids together with the non-osmotic secretion of ADH may result in hyponatraemia. Plasma electrolyte concentrations should be closely monitored in the paediatric population.

Effects on laboratory tests
The effect of this medicine on laboratory tests has not been established.

4.5 Interaction with other medicines and other forms of interaction

As for other calcium-containing infusion solutions, concomitant administration of ceftriaxone and Ringers solution for infusion is contraindicated in newborns (≤ 28 days of age), even if separate infusion lines are used (risk of fatal ceftriaxone-calcium salt precipitation in the neonate's bloodstream). In patients older than 28 days (including adults), ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions, including Ringers solution for infusion, through the same infusion line (e.g. via Y-connector). If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid.

Caution is advised in patients treated with medicines that may increase the risk of sodium and fluid retention, such as corticoids/steroids and carbenoxolone.

Ringers solution for infusion should be used with caution in patients treated concurrently or recently with agents or products that can cause hyperkalaemia or increase the risk of hyperkalaemia, such as potassium-sparing diuretics (amiloride, spironolactone, triamterene, alone or in association), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARAs), or the immunosuppressants tacrolimus and cyclosporine. Administration of potassium in patients treated with such agents is associated with an increased risk of severe and potentially fatal hyperkalaemia in

particular in the presence of other risk factors for hyperkalaemia, notably in case of a renal failure increasing the hyperkalaemic effect.

Administration of calcium may increase the effects of digitalis glycosides (digitalis cardiotonics) whose effects are enhanced by the presence of calcium and may lead to serious or fatal cardiac arrhythmia. In patients treated with digitalis glycosides, a reduction in the volume, and/or rate of administration may be warranted.

Caution is advised when administering Ringers solution for infusion to patients treated with medications leading to an increased vasopressin effect. The below listed medicines increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and may increase the risk of hyponatraemia following treatment with IV fluids (see sections 4.4 and 4.8).

- medicines stimulating vasopressin release such as chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors (SSRIs), 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, opioids,
- medicines potentiating vasopressin action such as chlorpropamide, non-steroidal anti-inflammatories (NSAIDS), cyclophosphamide,
- vasopressin analogues such as desmopressin, oxytocin, vasopressin, terlipressin.

Caution is advised when administering Ringers solution for infusion to patients treated with medicines that may increase the risk of hyponatraemia, such as diuretics and antiepileptics.

Ringers solution for infusion should be administered with caution in patients treated with thiazide diuretics or vitamin D as these can lead to hypercalcaemia.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

There are no adequate data for the use of Ringers solution for infusion in pregnant women. Ringers solution for infusion may be used during pregnancy as long as the electrolyte and fluid balance is controlled. However, physicians should carefully consider the potential risks and benefits for each specific patient before using Ringers solution for infusion in pregnant women.

When a medicinal product is added to Ringers solution for infusion, the nature of the medicine and its use during pregnancy have to be considered separately.

Breast-feeding

There are no adequate data for the use of Ringers solution for infusion in lactating women. Ringers solution for infusion may be used during lactation as long as the electrolyte and fluid balance is controlled. However, physicians should carefully consider the potential risks and benefits for each specific patient before using Ringers solution for infusion in lactating women.

When a medicinal product is added to Ringers solution for infusion, the nature of the medicine and its use during lactation have to be considered separately.

4.7 Effects on ability to drive and use machines

There is no information on the effects of Ringers solution for infusion on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

During the administration of Ringers solution for infusion, the following adverse reactions have been reported as very common (≥ 10%):

- hyperhydration and heart failure in patients with cardiac disorder or pulmonary oedema,
- electrolytes disturbances.

Adverse reactions may be associated to the technique of administration including febrile response, infection at the site of injection, local pain or reaction, vein irritation, venous thrombosis or phlebitis extending from the site of injection and extravasation.

The following adverse reactions have been reported in the post-marketing experience:
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Chills, Pyrexia.

Other adverse reactions reported with similar products:
METABOLISM AND NUTRITIONAL DISORDERS: Electrolyte imbalance, Fluid overload, Hyponatraemia.
NERVOUS SYSTEM DISORDERS: hyponatraemic encelophalopathy.

Adverse reactions may be associated to the medicinal product added to the solution; the nature of the additive will determine the likelihood of any other undesirable effects.

In case of undesirable effect(s), the infusion must be discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphv.otago.ac.nz/reporting/

4.9 Overdose

Excessive or too fast administration of Ringers solution for infusion can cause:

- Fluid and sodium overload with a risk of oedema (peripheral and/or pulmonary), particularly when renal sodium excretion is impaired. In such cases extra renal dialysis may be necessary.
- Hyperkalaemia, especially in patients with renal impairment. Symptoms include paresthesia of the extremities, muscle weakness, paralysis, cardiac arrhythmias, heart block, cardiac arrest, and mental confusion. Treatment of hyperkalaemia involves the administration of calcium, insulin (with glucose), sodium bicarbonate, exchange resins or dialysis.
- Hypercalaemia. Symptoms of hypercalaemia may include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, nephrocalcinosis, renal calculi, and, in severe cases, cardiac arrhythmias and coma. Too rapid intravenous injection of calcium salts may also lead to many of the symptoms of hypercalaemia as well as to a chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalaemia will usually resolve on stopping administration of calcium and other contributory medicines such as vitamin D. If hypercalaemia is severe, urgent treatment (such as loop diuretics, haemodialysis, calcitonin, bisphosphonates, trisodium edetate) is required.
- Hyperchloraemia.
- A loss of bicarbonate with an acidifying effect.

When assessing an overdose, any additives in the solution must be considered. When overdose is related to medicinal products added to the solution infused, the signs and symptoms of over infusion will be related to the nature of the additive being used.

The effects of an overdose may require immediate medical attention and treatment. Interventions include discontinuation of Ringers solution for infusion administration, dose reduction, and other measures as indicated for the specific clinical constellation.

The patient should be observed for the appropriate signs and symptoms related to the medicine administered. The relevant symptomatic and supportive measures should be provided as necessary.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Electrolytes.

ATC Code
B05BB01.

Mechanism of action
Ringers solution for infusion is an isotonic solution of electrolytes. The constituents of Ringers solution for infusion and their concentrations are designed to match those of plasma.

The pharmacodynamic properties of this solution are those of its components (water, sodium, potassium, calcium and chloride). The main effect of Ringers solution for infusion is for the expansion of the extracellular compartment including both the interstitial and intravascular fluids.

Ions, such as sodium, circulate through the cell membrane using various mechanisms of transport among which is the sodium pump (Na^+/K^+ ATPase). Sodium plays an important role in neurotransmission and cardiac electrophysiology, and also in its renal metabolism.

Potassium is essential for numerous metabolic and physiological processes including nerve conduction, muscle contraction, and acid-base regulation. A normal concentration of potassium in plasma is about 3.5 to 5.0mmoles per litre. Potassium is predominantly an intracellular cation, primarily found in muscle; only about 2% is present in the extracellular fluid. The passage of potassium into the cells and retention against the concentration gradient requires active transport via the Na^+/K^+ ATPase enzyme.

Approximately 99% of calcium is incorporated into the skeleton. The remaining 1% is found in body tissues and fluids, and is essential for normal nerve conduction, muscle activity, and blood coagulation.

Chloride is mainly an extracellular anion found in low concentration in bone and in high concentration in some components of connective tissue such as collagen. Intracellular chloride is in high concentration in red blood cells and gastric mucosa. The balance of anions and cations are regulated by the kidneys. Reabsorption of chloride generally follows reabsorption of sodium.

Clinical efficacy and safety
No data available.

Physiochemical properties

Chemical name	Molecular formular	Molecular weight	CAS number
Sodium chloride	NaCl	58.44	7647-14-5

Potassium chloride	KCl	74.55	7447-40-7
Calcium chloride dihydrate	$CaCl_2,2H_2O$	147.01	10035-04-8

Sodium chloride and potassium chloride occur as a colourless or white crystal and are freely soluble in water. Calcium chloride is a white, crystalline powder, hygroscopic and freely soluble in water.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of this solution are those of its components (sodium chloride, potassium chloride and calcium chloride).

The volume and the ionic composition of the extracellular and the intracellular compartments are as follows:

Extracellular fluid	approximately 19 litres
Sodium (mmol/L):	142
Potassium (mmol/L):	5
Calcium (mmol/L):	2.5
Chloride (mmol/L):	103
Intracellular fluid	approximately 23 litres
Sodium (mmol/L):	15
Potassium (mmol/L):	150
Calcium (mmol/L):	1
Chloride (mmol/L):	1

After injection of radiosodium (^{24}Na), the half-life is 11 to 13 days for 99% of the injected Na and one year for the remaining 1%. The distribution varies according to tissues: it is fast in muscles, liver, kidney, cartilage and skin; it is slow in erythrocytes and neurones; it is very slow in the bone. Sodium is predominantly excreted by the kidney, but there is extensive renal reabsorption. Small amounts of sodium are lost in the faeces and sweat.

Factors influencing potassium transfer between intracellular and extracellular fluid such as acid-base disturbances can distort the relationship between plasma concentrations and total body stores. Potassium is excreted mainly by the kidneys; it is secreted in the distal tubules in exchange of sodium or hydrogen ions. The capacity of the kidneys to conserve potassium is poor and some urinary excretion of potassium continues even when there is severe depletion. Some potassium is excreted in the faeces and small amounts may also be excreted in sweat.

The concentration of calcium in plasma is regulated by parathyroid hormone, calcitonin and vitamin D. About 47% of calcium in plasma is in the ionised physiologically active form, about 6% is complexed with anions such as phosphate or citrate, and the remainder is bound to proteins, principally albumin. If the plasma-albumin concentration is raised (as in dehydration) or reduced (as is common in malignancy) it will affect the proportion of ionised calcium. Thus, the total plasma-calcium concentration is commonly adjusted for plasma albumin. Excess of calcium is predominantly excreted renally. Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice. Minor amounts are lost in the sweat, skin, hair and nails. Calcium crosses the placenta and is distributed into breast milk.

5.3 Preclinical safety data

Genotoxicity

The active ingredients potassium chloride, sodium chloride and calcium chloride are not mutagenic at physiological concentrations.

Carcinogenicity
The active ingredients potassium chloride, sodium chloride and calcium chloride are not carcinogenic at physiological concentrations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections
Hydrochloric acid and/or sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

Compatibility may vary between products from different sources and healthcare professionals are advised to carry out appropriate checks when mixing Ringers solution for infusion with other parenteral solutions.

Ringers solution for infusion is incompatible with the following agents due to precipitate formation:

- amphotericin B,
- cortisone,
- erythromycin lactobionate,
- ethyl alcohol,
- thiopental sodium, and
- disodium edetate.

6.3 Shelf life

24 months from date of manufacture.

The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at or below 30°C.

Exposure of pharmaceutical products to heat should be minimised. Avoid excessive heat.

6.5 Nature and contents of container

Ringers solution for infusion is supplied in Viaflex plastic containers as a single unit dose as shown in the following table:

Code No.	Name of the active components [Concentrations (%, mmol/1000mL)]	Osmolality (mOsmol/kg)	Registration no.	Pack sizes* (mL)
AHB2304	Potassium Chloride (0.03%, 4) Sodium Chloride (0.86%, 147) Calcium Chloride (0.033%, 2.2)	308	TT50-5550	1000 (x 12 bags)
AHB2303				500
Note: Not all pack sizes may be marketed.				

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

Ringers solution for infusion is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Ringers solution for infusion is distributed in Australia by:
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
6 September 1977.

10 DATE OF REVISION OF THE TEXT

1 May 2019.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
ALL	Pharmaceutical form corrected throughout document. Consistent use of bullet points and formatting.
2	Reference to section 6.1 for excipients added.
3	Appearance of solution added.
4.2	Sterile preparation requiring aseptic technique, added to preparation for administration section.
4.4	Added information relating to special warnings and precautions for use
4.5	Added information relating to interaction with other medicines
4.7	Added information relating to ability to drive and use machinery
4.8	Added adverse reactions information reported with similar products
5.1	Pharmacodynamic information amended.
6.2	Compatibility information moved from 4.2 to this section.
6.3	Added that expiry date can be located on packaging.

Based on Australian PI most recent amendment 30 April 2019 and CCSI454 2018 0628.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.