Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ringer's Solution for Infusion, Viaflo container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium chloride:	8.60	g/L
Potassium chloride:	0.30	g/L
Calcium chloride dihydrate:	0.33	g/L

mmol/l:	Na^+: 147	K^+: 4	Ca^{++}: 2.25	Cl^-: 155.50
mEq/l:	Na^+: 147	K^+: 4	Ca^{++}: 4.50	Cl^-: 155.50

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear solution, free from visible particles.
Osmolarity: 309 mOsm/l (approx) pH: 5.0 to 7.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ringer's Solution for Infusion is indicated to:

- Replace extracellular fluid losses,
- Restore the sodium, potassium, calcium and chloride balances, for treatment of isotonic dehydration

4.2 Posology and method of administration

Posology

Adults, the Elderly, Adolescents and Children:
Fluid balance, serum electrolytes and acid-base balance may need to be monitored before and during administration, with particular attention to serum sodium in patients with increased non-osmotic vasopressin release (syndrome of inappropriate antidiuretic hormone secretion, SIADH) and in patients co-medicated with vasopressin agonist drugs, due to the risk of hospital acquired hyponatraemia (see sections 4.4, 4.5 and 4.8). Monitoring of serum sodium is particularly important for hypotonic fluids.

Ringer's Solution tonicity: Isotonic solution

The infusion rate and volume depend on the age, weight, clinical condition (e.g. burns, surgery, head-injury, infections), and concomitant therapy should be determined by the consulting physician experienced in paediatric intravenous fluid therapy (see sections 4.4. and 4.8).

Recommended dosage:
The recommended dosage is:
- for adults, the elderly and adolescents: 500 ml to 3 *litres* /24h
- for babies and children: 20 ml to 100 ml / kg / 24 h.

Administration rate:

The infusion rate is usually 40 ml/kg/24h in adults, the elderly and adolescents.
In paediatric patients the infusion rate is 5 ml/kg/h on average but the value varies with age: 6-8 ml/kg/h for infants, 4-6 ml/kg/h for toddlers, and 2-4 ml/kg/h for schoolchildren. In children with burns, the dose is on average 3.4 ml/kg/per cent burn at 24 h post-burn and 6.3 ml/kg/per cent burn at 48 h.
In severely head-injured children the dose is on average 2850 ml/m^2.
Infusion rate and total volume can be higher in surgery or in case of need.

Note:
infants and toddlers: aged from 28 days to 23 months (a toddler is an infant who can walk)
- *children and schoolchildren: aged from 2 years to 11 years.*

Method of administration:
The administration is performed by intravenous route.

The solution for infusion should be visually inspected prior to use.
Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following the insertion of infusion set. Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the product.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.
Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.
Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.
The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.
Additives may be introduced before infusion or during infusion through the injection site.

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

4.3 Contraindications

The solution is contraindicated in patients presenting with:

- Extracellular hyperhydration or hypervolemia
- Hypertonic dehydration
- Hyperkalemia
- Hypernatremia
- Hypercalcaemia
- Hyperchloraemia
- Severe renal insufficiency (with oliguria/anuria).
- Uncompensated cardiac failure
- Severe hypertension
- General oedema and ascitic cirrhosis
- Concomitant digitalis therapy (see section 4.5)

As for other calcium-containing infusion solutions , treatment with ceftriaxone and Ringer's Solution for Infusion is contraindicated in preterm newborn infants and term newborn infants (≤ 28 days of age), even if separate infusion lines are used (risk of fatal ceftriaxone calcium salt precipitation in the neonate's bloodstream).

4.4 Special warnings and precautions for use

Ringer's Solution for Infusion contains insufficient concentration 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.

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

Depending on the volume and rate of infusion, intravenous administration of Ringer's Solution can cause fluid retention and or/solute overload resulting in overhydration and for example, congested states, including pulmonary congestion and edema.

Solutions containing sodium chloride should be administered with caution to patients with hypertension, heart failure, peripheral or pulmonary oedema, impaired renal function, pre-eclampsia, aldosteronism or other conditions or treatment (e.g. corticoids/steroids) associated with sodium retention (see also Section 4.5 – Interactions with other medicinal products and other forms of interaction).

Solutions containing potassium salts should be administered with caution to patients with cardiac disease, or conditions predisposing to hyperkalemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns.

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.

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 (see below).

Hyponatraemia

Patients with non-osmotic vasopressin release (e.g. in acute illness, pain, post-operative stress, infections, burns, and CNS diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists (see section 4.5) are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

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

Children, women in the fertile age and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding, cerebral contusion and brain oedema) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

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 calcium renal calculi or a history of such calculi or diseases associated with elevated vitamin D concentrations such as sarcoidosis
- in case of concomitant blood transfusion, the solution must not be administered via the same infusion set because of the risk of coagulation.

Calcium-Ceftriaxone precipitates

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborn infants aged less than 1 month have been described.
In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions even via different infusion lines or different infusion sites

However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. Sequential infusions of ceftriaxone and calcium-containing products must be avoided in case of hypovolaemia.

Renal Function

Ringer's Solution should be administered with particular caution, to patients with or risk of severe renal impairment. In such patients, administration of Ringer's Solution may result in electrolyte abnormalities.

For information on preparation of the product and additives, please see section 6.6.

Pediatric use

Plasma electrolyte concentrations should be closely monitored in the pediatric population.

Elderly

When selecting the type of infusion solution and the volume/rate of infusion for an elderly patient, consider that elderly patients are generally more likely to have cardiac, renal, hepatic, and/or other diseases, and/or concomitant drug therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with ceftriaxone

- Concomitant treatment with ceftriaxone and Ringer's Solution for Infusion is contraindicated in preterm newborn infants and term newborn infants (≤28 days of age), even if separate infusion lines are used (risk of fatal ceftriaxone-calcium salt precipitation in the neonate's bloodstream) (see Section 4.3).
- In patients older than 28 days (including adults), ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions, including Ringer's Solution for Infusion (See Section 4.4) even via different infusion lines or different infusion sites (see section 6.2).

Interaction related to the presence of sodium:

- Corticoids/Steroids and carbenoxolone, which are associated with the retention of sodium and water (with oedema and hypertension).

Interaction related to the presence of potassium:

- Potassium-sparing diuretics (amiloride, spironolactone, triamterene, alone or in association),
- Angiotensin converting enzyme inhibitors (ACEI) and, by extrapolation, angiotensin II receptor antagonists
- Tacrolimus, cyclosporine which increase concentration of potassium in the plasma and may lead to potentially fatal hyperkalaemia notably in case of a renal failure increasing the hyperkalaemic effect

Interaction related to the presence of calcium:

- Digitalis glycosides (digitalis cardiotonics) whose effects are enhanced by the presence of calcium and may lead to serious or fatal cardiac arrhythmia (see section 4.3)
- Thiazide diuretics or vitamin D which can lead to hypercalcaemia when co-administered with calcium.

Drugs leading to an increased vasopressin effect.

The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and may increase the risk of hospital acquired hyponatraemia following inappropriately balanced treatment with i.v. fluids (see sections 4.2, 4.4 and 4.8).

- Drugs stimulating vasopressin release include: Chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics
- Drugs potentiating vasopressin action include: Chlorpropamide, NSAIDs, cyclophosphamide
- Vasopressin analogues include: Desmopressin, oxytocin, vasopressin, terlipressin

Other medicinal products increasing the risk of hyponatraemia also include diuretics in general and antiepileptics such as oxcarbazepine.

For information on incompatibilities between this and other products, please see section 6.2.

4.6 Fertility, pregnancy and lactation

Ringer's Solution for infusion can be used safely during pregnancy and lactation as long as the electrolyte and fluid balance is controlled.

When a medicinal product is added, the nature of the drug and its use during pregnancy and lactation have to be considered separately.

Ringer's Solution should be administrated with special caution for pregnant women during labour particularly as to serum-sodium if administered in combination with oxytocin (see section 4.4, 4.5 and 4.8).

4.7 Effects on ability to drive and use machines

There is no information on the effect of Ringer's Solution on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

Tabulated list of adverse reactions

MedDRA System Organ Class	**Adverse Reactions** ***(Preferred term)***	**Frequency**
Metabolism and nutrition disorders	Hyperhydration* Electrolytes disturbances Hospital acquired hyponatraemia**	Very common Very common Not known
Cardiac disorders	Heart failure*	Very common
Nervous system Disorders	Acute hyponatraemic encephalopathy**	Not known

** in patients with cardiac disorder or pulmonary oedema*
***Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy*

Fluid overload, hypersensitivity and urticaria have been reported with other similar solutions.
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.
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 adverse reactions.
In case of adverse reaction(s), the infusion must be discontinued.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdose or too fast administration may lead to water and sodium overload with a risk of oedema, particularly when there is a defective renal sodium excretion. In this case extra renal dialysis may be necessary.

Excessive administration of potassium may lead to the development of *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.

Excessive administration of calcium salts may lead to *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 drugs such as vitamin D. If *hypercalaemia* is severe, urgent treatment (such as loop diuretics, *haemodialysis*, calcitonin, bisphosphonates, trisodium edetate) is required.

Excessive administration of chloride salts may cause hyperchloremia and a loss of bicarbonate with an acidifying effect.
The effects of an overdose may require immediate medical attention and treatment. Interventions include discontinuation of Ringer's Solution administration, dose reduction, and other measures as indicated for the specific clinical constellation.

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.

In the event of accidental over infusion, treatment should be discontinued and the patient should be observed for the appropriate signs and symptoms related to the drug administered. The relevant symptomatic and supportive measures should be provided as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: "Electrolytes", ATC code: B05BB01"

Ringer's Solution for Infusion is an isotonic solution of electrolytes. The constituents of Ringer's 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 Ringer's Solution for Infusion is 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 5.0 mmoles 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.

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:

<u>Extracellular fluid: approximately 19 liters</u>	
Sodium (mmol/l):	142.00
Potassium (mmol/l):	5.00
Calcium (mmol/l):	2.50
Chloride (mmol/l):	103.00
<u>Intracellular fluid: approximately 23 liters</u>	
Sodium (mmol/l):	15.00
Potassium (mmol/l):	150.00

Calcium (mmol/l):	1.00
Chloride (mmol/l):	1.00

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 feces 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 feces 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 ionized 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 ionized 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 feces, 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

Preclinical safety data of Ringer's solution for infusion in animals are not relevant since its constituents are physiological components of animal and human plasma.

Toxic effects are not to be expected under the condition of clinical application.

The safety of potential additives should be considered separately.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Incompatibility of the medicinal product to be added with the solution in Viaflo container must be assessed before addition.
Ceftriaxone: See sections 4.3 and 4.4 for more information

In the absence of compatibility studies, this solution must not be mixed with other medicinal products.
The Instructions for Use of the medicinal product to be added must be consulted.Before adding a drug, verify it is soluble and stable in water at the pH of Ringer's Solution for Infusion (see section 3).
Calcium salts have been reported to be incompatible with a wide range of drugs. Complexes may form resulting in the formation of a precipitate.
As a guidance, the following medications are incompatible with the Ringer's Solution (non-exhaustive listing):

- Amphotericin B
- Cortisone
- Erythromycin lactobionate
- Etamivan
- Ethyl alcohol
- Thiopental sodium
- Disodium edetate

Those additives known to be incompatible should not be used.

6.3 Shelf life

Unopened: 500 ml: 24 months
1000 ml: 36 months

In-use shelf life:

Chemical and physical stability of any additive at the pH of the Ringer's Solution in the Viaflo container should be established prior to use.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The bags are composed of polyolefin/polyamide co-extruded plastic (PL 2442). The bags are overwrapped with a protective plastic pouch composed of polyamide/polypropylene, which serves only to provide physical protection to the bags.

The bag size is either 500 or 1000 ml. *(Not all pack sizes may be marketed)*
Outer carton contents:

- 1 bag of 500 ml
- 20 bags of 500 ml
- 1 bag of 1000 ml
- 10 or 12 bags of 1000 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Discard after single use.
Discard any unused portion.
Do not reconnect partially used bags.

Opening

● Remove the Viaflo container from the overpouch just before use.
● Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution, as sterility may be broken.
● Check the solution for limpidity and absence of foreign matters. If solution is not clear or contains foreign matters, discard the solution.

Preparation for administration

Use sterile material for preparation and administration.

● Suspend container from eyelet support.
● Remove plastic protector from outlet port at bottom of container:
  - grip the small wing on the neck of the port with one hand,
  - grip the large wing on the cap with the other hand and twist,
  - the cap will pop off.
● Use an aseptic method to set up the infusion

● Attach administration set. Refer to complete directions accompanying set for connection, priming of the set and administration of the solution.

Techniques for injection of additive medication

Warning: Additives may be incompatible.
When additive is used, verify isotonicity prior to parenteral administration. Thorough and careful aseptic mixing of any additive is mandatory. Solutions containing additives should be used immediately and not stored.

To add medication before administration

● Disinfect 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, tap the ports gently while ports are upright and mix.

Caution: Do not store bags containing added medications.

To add medication during administration

● Close clamp on the set.
● Disinfect 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 an upright position.
● Evacuate both ports by tapping gently while the container is in an upright position.
● Mix solution and medication thoroughly.
● Return container to in use position, re-open the clamp and continue administration.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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