Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Compound Sodium Lactate Solution for Infusion BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium Chloride: 6.00 g/l
Potassium Chloride: 0.40 g/l
Calcium Chloride dihydrate: 0.27 g/l
Sodium Lactate: 3.20 g/l

	Na^+	K^+	Ca^{++}	Cl^-	$C_3H_5O_3^-$ (lactate)
mmol/l	131	5	2	111	29
mEq/l	131	5	4	111	29

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear solution, free from visible particles.
278 mOsm/l (approx.) pH: 5.0 – 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Compound Sodium Lactate solution is used in the following indications:

- Restoration of extracellular fluid and electrolytes balances or replacement of extracellular fluid loss where isotonic concentrations of electrolytes are sufficient
- Short term volume replacement (alone or in association with colloid) in case of hypovolaemia or hypotension.
- Regulation or maintenance of metabolic acidosis balance and/or treatment of mild to moderate metabolic acidosis (except lactic acidosis)

4.2 Posology and method of administration

Posology
Adults, the Elderly and Children:
Dosage, rate, and duration of administration are to be individualized and depend upon the indication for use, the patient's age, weight, clinical condition, and concomitant treatment, and on the patient's clinical and laboratory response to treatment.

Recommended dosage:
The amount of Compound Sodium Lactate solution (Ringer Lactate solution) needed to restore normal blood volume is 3 to 5 times the volume of lost blood.

The recommended dosage is:
- for adults : 500 ml to 3 L / 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.

Use in paediatric patients

The safety and efficacy of Compound Sodium Lactate solution in children has not been established by adequate and well-controlled trials; however, the use of electrolyte solutions in the paediatric population is referenced in the medical literature. Lactate-containing solutions should be administered with particular caution to neonates and infants less than 6 months of age.

Paediatric infusion rates is 5 ml/kg/h in average but the valuevaries with age:
•infants: 6-8 mL/kg/h,
•toddlers: 4-6 mL/kg/h
•children: 2-4 mL/kg/h .

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: age from 2 to 11 years

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

Method of Administration:
The solution is for intravenous administration through a sterile and non-pyrogenic administration set using aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.
The solution should be inspected visually for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear, free from visible particles and the seal is intact. Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the solution. Administer immediately following the insertion of infusion set.

Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container. 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.

Additives may be introduced before infusion or during infusion through the injection site. When making additions to Compound Sodium Lactate solution, aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives.
For information on incompatibilities and preparation of the product with additives, please see sections 6.2 and 6.6.

4.3 Contraindications

As for other calcium-containing infusion solutions, concomitant administration of ceftriaxone and Compound Sodium Lactate solution 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). For patients over 28 days of age please see section 4.4.

Compound Sodium Lactate solution is also contraindicated in patients with

- A known hypersensitivity to sodium lactate.
- Extracellular hyperhydration or hypervolemia
- Severe renal insufficiency (with oliguria/anuria)
- Uncompensated cardiac failure
- Hyperkalaemia
- Hypercalcaemia
- Metabolic alkalosis
- Ascitic cirrhosis
- Severe metabolic acidosis

- Conditions associated with increased lactate levels (hyperlactatemia) including lactic acidosis, or impaired lactate utilization, such as severe hepatic insufficiency.
- Concomitant digitalis therapy (see section 4.5 Interactions with other medicinal products and other forms of interaction)

4.4 Special warnings and precautions for use

Hypersensitivity reactions
The infusion must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Incompatibilities
Ceftriaxone
In patients older than 28 days (including adults), ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions, including Compound Sodium Lactate solution, through the same infusion line. If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid. For patients under 28 days please see section 4.3.

Electrolyte balance
Hypernatraemia
Compound Sodium Lactate solution should only be administered to patients with hypernatraemia after careful consideration of the underlying cause and alternative intravenous fluids. Monitoring of plasma sodium and volume status during treatment is recommended.
Compound Sodium Lactate solution should be administered with particular caution in patients with conditions predisposing to hypernatraemia (such as adrenocortical insufficiency, diabetes insipidus or extensive tissue injury) and in patients with cardiac disease.

Hyperchloraemia
Compound Sodium Lactate solution should only be administered to patients with hyperchloraemia after careful consideration of the underlying cause and alternative intravenous fluids. Monitoring of plasma chloride and acid-base balance during treatment is recommended.
Compound Sodium Lactate solution should be administered with particular caution to patients with conditions predisposing to hyperchloraemia (such as renal failure and renal tubular acidosis, diabetes insipidus), and patients with urinary diversion or patients taking certain diuretics (carbonic anhydrase inhibitors eg acetazolamide) or steroids (androgens, estrogens corticosteroids) and in patients with severe dehydration.

Use in patients with potassium deficiency
Although Compound Sodium Lactate solution has a potassium concentration similar to the concentration in plasma, it is insufficient to produce a useful effect in case of severe potassium insufficiency and therefore it should not be used for this purpose.

Use in patients at risk for hyperkalaemia
Compound Sodium Lactate solution should be administered with particular caution to patients with conditions predisposing to hyperkalaemia (such as severe renal impairment or adrenocortical insufficiency, acute dehydration, or extensive tissue injury or burns) and in patients with cardiac disease. The plasma potassium level of the patient must be particularly closely monitored in patients at risk of hyperkalaemia.

Use in patients at risk for hypercalcaemia
Calcium chloride is irritant, therefore care should be taken to prevent extravasation during intravenous injection and intramuscular injection must be avoided. Solutions containing calcium salts should be used with caution in patients with conditions predisposing to hypercalcaemia, such as patients with renal impairment and granulomatous diseases associated with increased calcitriol synthesis such as sarcoidosis, calcium renal calculi or a history of such calculi.

Fluid balance/renal function
Use in patients with renal impairment
Compound Sodium Lactate solution should be administered with particular caution to patients with renal impairment. In such patients administration of Compound Sodium Lactate solution may result in sodium and/or potassium retention.

Risk of Fluid and/or Solute Overload and Electrolyte Disturbances

Depending on the volume and rate of infusion, intravenous administration of Compound Sodium Lactate solution 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.
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.

Use in patients with hypervolaemia, overhydration or conditions causing sodium retention and edema

Compound Sodium Lactate solution should be administered with particular caution to hypervolaemic or overhydrated patients.
Due to the sodium chloride content Compound Sodium Lactate solution should be administered with particular caution to patients with conditions that may cause sodium retention, fluid overload and oedema, such as patients with primary hyperaldosteronism, secondary hyperaldosteronism (associated with, e.g., hypertension, congestive heart failure, renal artery stenosis, or nephrosclerosis), or preeclampsia.(see also Section 4.5)

Acid-base balance

Use in patients at risk for alkalosis

Compound Sodium Lactate solution should be administered with particular caution to patients at risk for alkalosis. Because lactate is metabolized to bicarbonate, administration may result in, or worsen, metabolic alkalosis. Seizure may be precipitated by the alkalosis induced by lactate but this is uncommon.

Other warnings

Administration of citrate anticoagulated/preserved blood

Due to the risk of coagulation precipitated by its calcium content, Compound Sodium Lactate solution must not be added to or administered simultaneously through the same tubing with citrate anticoagulated/preserved blood.

Use in patients with type 2 diabetes

Lactate is a substrate for gluconeogenesis. Therefore glucose levels should be carefully monitored in patients receiving Compound Sodium Lactate.

Administration

Adding other medication or using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In such case the infusion must be stopped immediately.

For information on incompatibilities and preparation of the product with additives, please see sections 6.2 and 6.6.

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

4.5 Interaction with other medicinal products and other forms of interaction

Ceftriaxone: See sections 4.3 and 4.4 for more information

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, terlipressin

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

Interaction related to the presence of sodium:

Caution is advised when administering Compound Sodium Lactate solution to patients treated with drugs that may increase the risk of sodium and fluid retention (with oedema and hypertension), such as corticosteroids.

Interaction related to the presence of potassium:

Because of its potassium content, Compound Sodium Lactate solution should be administered with caution in patients treated 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 inhibitors (ACEi) and angiotensin II receptor antagonists
- Tacrolimus, cyclosporine

Administration of potassium in patients treated with such medications can produce severe and potentially fatal hyperkalaemia, particularly in patients with severe renal insufficiency.

Interaction related to the presence of calcium:

Administration of calcium may increase the effects of digitalis and lead to serious or fatal cardiac arrhythmia. Therefore, larger volumes or a faster infusion rates should be used with caution in patients treated with digitalis glycosides.

- Caution is advised when administering Compound Sodium Lactate solution to patients treated with thiazide diuretics or vitamin D, as these can increase the risk of hypercalcaemia.
- Bisphosphonates, fluoride, some fluoroquinolones and tetracyclines which are less absorbed (lower availability) when administered with calcium.

Interaction related to the presence of lactate (which is metabolized into bicarbonate):

Caution is advised when administering Compound Sodium Lactate solution to patients treated with drugs for which renal elimination is pH dependent. Due to the alkalinizing action of lactate (formation of bicarbonate), Compound Sodium Lactate solution may interfere with the elimination of such drugs.

- Renal clearance of acidic drugs such as salicylates, barbiturates, and lithium may be increased because of the alkalinisation of urine by the bicarbonate resulting from lactate metabolism.
- Renal clearance of alkaline drugs, such as sympathomimetics (e.g. ephedrine, pseudoephedrine) and stimulants (e.g. dexamphetamine sulfate, phenfluramine hydrochloride) may be decreased

4.6 Fertility, pregnancy and lactation

Compound Sodium Lactate solution can be used safely during pregnancy and lactation as long as the electrolyte- and fluid balance is controlled.
It is reminded that calcium crosses the placenta and is distributed into breast milk.

Compound Sodium Lactate 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).

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

4.7 Effects on ability to drive and use machines

There is no information of the effects of Compound Sodium Lactate solution on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

The following adverse reactions (listed by MedDRA System Organ Class) have been reported spontaneously during the post-market experience.

Immune System Disorders	Hypersensitivity/Infusion reactions including Anaphylactic/Anaphylactoid reaction, possibly manifested by one or more of the following symptoms: Angioedema, Chest pain, Chest discomfort, Decreased heart rate, Tachycardia, Blood pressure decreased, Respiratory distress, Bronchospasm, Dyspnea, Cough, Urticaria, Rash, Pruritus, Erythema, Flushing, Throat irritation, Paresthesias, Hypoesthesia oral, Dysgeusia, Nausea, Anxiety, Pyrexia, Headache
Metabolism and Nutrition Disorders	Hyperkalaemia
General Disorders and Administration Site Conditions	Infusion Site Reactions manifested by one or more of the following symptoms: Phlebitis, Infusion site inflammation, Infusion site swelling, Infusion site rash, Infusion site pruritus, Infusion site erythema, Infusion site pain, Infusion site burning

The following adverse reactions have been reported spontaneously during the use of other sodium-lactate containing solutions:
- Hypersensitivity: Laryngeal oedema (Quincke's oedema), skin swelling, Nasal congestion, Sneezing
- Electrolyte disturbances
- Hypervolaemia
- Panic Attack
- Other infusion site reactions: Infection at the site of injection, Extravasation, Infusion site anesthesia (numbness)

4.9 Overdose

An excessive volume or too high a rate of administration of Compound Sodium Lactate solution may lead to fluid and sodium overload with a risk of edema (peripheral and/or pulmonary), particularly when renal sodium excretion is impaired. 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.

Excessive administration of calcium salts may lead to hypercalcemia. Symptoms of hypercalcaemia 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 hypercalcaemia as well as to chalky taste, hot flushes, and peripheral vasodilatation.
Mild asymptomatic hypercalcaemia will usually resolve on stopping administration of calcium and other contributory drugs such as vitamin D. If hypercalcemia is severe, urgent treatment (such as loop diuretics, hemodialysis, calcitonin, bisphosphonates, trisodium edetate) is required.

Excessive administration of lactate may lead to metabolic alkalosis. Metabolic alkalosis may be accompanied by hypokalaemia, Symptoms may include mood changes, tiredness, shortness of breath, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop especially in hypocalcaemic patients. Treatment of metabolic alkalosis due to bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium may be of particular importance.

When overdose is related to medications 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 (ATC code): B05BB01 “Electrolytes” Compound Sodium Lactate solution (Ringer Lactate solution) is an isotonic solution of electrolytes. The constituents of Compound Sodium Lactate (Ringer Lactate) and their concentrations are designed to match those of plasma.

The pharmacological properties of the Compound Sodium Lactate solution (Ringer Lactate solution) are those of its components (sodium, potassium, calcium, chloride and lactate). The main effect of Compound Sodium Lactate (Ringer Lactate) is the expansion of the extracellular compartment including both the interstitial fluid and the intravascular fluid.
The lactate is metabolised into bicarbonate, mainly in the liver, and produces an alkalinising effect on the plasma.
In healthy volunteers receiving Compound Sodium Lactate(Ringer Lactate), central venous pressure changes were associated with a secretion of atrial natriuretic peptide.

In healthy volunteers, Compound Sodium Lactate (Ringer Lactate) decreased serum osmolality, increased blood pH, and the time until first urination was shorter than that with normal saline.
There is no significant changes in glucagon, norepinephrine, epinephrine, blood glucose and insulin levels in aortic surgery patients receiving Compound Sodium Lactate(Ringer Lactate).
When medication is added to Compound Sodium Lactate (Ringer Lactate), the overall pharmacodynamics of the solution will depend on the nature of the drug used.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the Compound Sodium Lactate solution (Ringer Lactate solution) are those of the ions its composition includes (sodium, potassium, calcium and chloride).
Infusion of Compound Sodium Lactate (Ringer Lactate) in normal hemodynamically stable adults does not increase circulating lactate concentrations.

The pharmacokinetics of D-lactate and L-lactate are similar.
The lactate in Compound Sodium Lactate solution (Ringer Lactate solution) is metabolized by both oxidation and gluconeogenesis, predominantly in the liver, and bicarbonate is generated by both processes over 1-2 h.
When medication is added to Compound Sodium Lactate (Ringer Lactate), the overall pharmacokinetics of the solution will depend on the nature of the drug used.

5.3 Preclinical safety data

Preclinical safety data of Compound Sodium Lactate (Ringer Lactate) solution in animals are not relevant since its constituents are physiological components in 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

Water for injections

6.2 Incompatibilities

Ceftriaxone must not be mixed with calcium-containing solutions including Compound Sodium Lactate solution. See also section 4.3 and 4.4.
As with all parenteral solutions additives may be incompatible. Compatibility of the additives with the Compound Sodium lactate solution and Viaflo container must be assessed before addition. After addition of the additive, incompatibility may become visible by a possible colour change and/or the appearance of precipitates, insoluble complexes or crystals.
The Instructions for Use of the medication to be added and other relevant literature must be consulted.
Before adding a substance or medication, verify that it is soluble and/or stable in water and that the pH range of Compound Sodium Lactate solution is appropriate (pH 5.0 to 7.0).
When making additions to Compound Sodium Lactate solution, aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives.
As a guidance the following medications are incompatible with the Compound Sodium Lactate solution (***non-exhaustive listing***):

Medications incompatible with Compound Sodium Lactate Solution
Aminocaproic acid
Amphotericin B
Metaraminol tartrate
Cefamandole
Ceftriaxone
Cortisone acetate
Diethylstilbestrol
Etamivan
Ethyl alcohol
Phosphate and carbonate solutions
Oxytetracycline
Thiopental sodium
Versenate disodium
Medications with partial incompatibility with Compound Sodium Lactate Solution:
Tetracycline stable for 12 hours
Ampicillin sodium
concentration of 2%-3% stable for 4 hours
concentration >3% must be given within 1 hour
Minocycline stable for 12 hours
Doxycycline stable for 6 hours

Additives known or determined to be incompatible should not be used.

6.3 Shelf life

Shelf life (Unopened):
3 years for the 1000 ml container
2 years for the 500 ml container
18 months for the 250ml container

In-use shelf-life: Additives
Chemical and Physical stability of any additive at the pH of Compound Sodium Lactate solution (Ringer Lactate solution) in the Viaflo container should be established prior to use.
From a microbiological point of view, the diluted product must be used immediately unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

250ml: Do not store above 30°C
500ml and 1000ml: No special precautions for storage.

6.5 Nature and contents of container

The bags known as Viaflo are composed of polyolefin/polyamide co-extruded plastic.

Bag sizes: 250ml, 500ml and 1000ml.

The bags are overwrapped with a protective plastic pouch composed of polyamide/polypropylene.

Pack sizes:

- 30 bags of 250 ml per carton
- 1 bag of 250 ml
- 20 bags of 500 ml per carton
- 1 bag of 500 ml
- 10 bags of 1000 ml per carton

- 12 bags of 1000 ml per carton
- 1 bag of 1000 ml

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

After opening the container, the contents should be used immediately and should not be stored for a subsequent infusion.
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 impaired
•Check the solution for clarity and absence of foreign matter. If solution is not clear or contains foreign matter, 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:
  - o grip the small wing on the neck of the port with one hand
  - o grip the large wing on the cap with the other hand and twist,
  - o the cap will pop off.

•Use an aseptic method to set up the infusion.
•Attach administration set. Refer to directions accompanying set for connection, priming of the set and administration of the solution.

Techniques for injection of additive medications
Warning: Some additives may be incompatible. Check additive compatibility with both the solution and container prior to use. 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 gauge (1.10 mm) to 22 gauge (0.70 mm) 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 gauge (1.10 mm) to 22 gauge (0.70 mm) 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

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