SUMMARY OF PRODUCT CHARACTERISTICS

COMPOUND SODIUM LACTATE BP (HARTMANN'S SOLUTION)

SOLUTION FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT

Compound Sodium Lactate BP (Hartmann's Solution)

(Synonyms: - Ringer Lactate Solution for Infusion
- Hartmann's Solution for Infusion)

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 the 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

- Source of water and electrolytes.
- Regulation or maintenance of metabolic acidosis (except lactic acidosis).

4.2. Posology and Method of Administration

Posology

Adults, the elderly and children:

The dosage depends on the age, weight, clinical and biological (acid-base balance) conditions of the patient, and concomitant therapy.

Recommended dosage:

The amount of Compound Sodium Lactate BPsolution (Hartmann's 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.
In pediatric 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/m².
Infusion rate and total volume can be higher in surgery or in case of need.

Note:
- infants and toddlers: age ranges from about 28 days to 23 months (a toddler is an infant who can walk)
- children and shoolchildren: age ranges from about 2 years to 11 years.

Administration:

The administration is performed by intravenous route using sterile and non-pyrogenic equipment.

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 hypervolaemia
- Severe renal insufficiency (with oliguria/anuria)
- Uncompensated cardiac failure
- Hyperkalaemia
- Hypercalcaemia
- Metabolic alkalosis
- Ascitic cirrhosis
- Severe metabolic acidosis
- Conditions associated with increased lactate levels (hyperlactataemia) 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, e.g., 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 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.

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

This medicinal product contains 301.3 mg sodium per 100 ml, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicine contains 0.5 mmol (or 19.5 mg) potassium per 100 ml. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

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 4.4 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, cyclosporin.

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 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 on 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 Hospital acquired hyponatraemia*
Nervous System Disorders	Acute hyponatraemic encephalopathy*
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

*Hospital acquired hyponatraemia may cause irreversible brain injury and death, due to development of acute hyponatraemic encephalopathy, frequency unknown (see sections 4.4 and 4.5).

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)

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

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 oedema (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 hypercalcaemia. 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 hypercalcaemia is severe, urgent treatment (such as loop diuretics, haemodialysis, 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 solution (Ringer Lactate solution) 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 solution (Ringer Lactate solution) 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 solution (Ringer Lactate solution), central venous pressure changes were associated with a secretion of atrial natriuretic peptide.
In healthy volunteers, Compound Sodium Lactate solution (Ringer Lactate solution) 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 solution (Ringer Lactate solution).
When medication is added to Compound Sodium Lactate solution (Ringer Lactate solution), 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 solution (Ringer Lactate solution) 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 solution (Ringer Lactate solution), 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 solution (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 Injection.

6.2. Incompatibilities

Ceftriaxone must not be mixed with calcium-containing solutions including Compound Sodium Lactate solution. See also sections 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): The expiry date of the product is indicated on the packaging materials.

In-use shelf-life: Additives

Chemical and physical stability of any additive at the pH of Compound Sodium 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

Store below 25°C.

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.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

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:

- 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 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. LICENCE HOLDER AND MANUFACTURER

Licence holder:

Teva Israel Ltd, 124 Dvora HaNevi'a St, Tel Aviv 6944020 Israel

Manufacturer:

Baxter Healthcare Ltd.
Thetford,
United Kingdom

8. REGISTRATION NUMBER

144.58.33070

The leaflet was revised in September 2022 acording to the MOHs guidelines