SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Compound Sodium Lactate Intravenous Infusion BP

(Hartmann's Solution)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml of solution contain

Sodium chloride	6.00 g
Sodium lactate solution (50% w/w) (equivalent to sodium lactate, 3.12 g)	6.24 g
Potassium chloride	0.40 g
Calcium chloride dihydrate	0.27 g

Electrolyte concentrations:

Sodium	131 mmol/l
Potassium	5.4 mmol/l
Calcium	1.8 mmol/l
Chloride	112 mmol/l
Lactate	28 mmol/l

Excipients

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion,
Clear, colourless aqueous solution

Theoretical osmolarity: 277 mOsm/l
Acidity (titration to pH 7.4): < 1 mmol/l
pH: 5.0 – 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Because of its close resemblance to the plasma mineral content, Compound Sodium Lactate Intravenous Infusion is used as fluid and electrolytes replacement.

4.2 Posology and method of administration

Posology

The dosage depends on age, weight and clinical condition of the patient.

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

General guideline for adults:
Average dose: 1000 ml/day
Flow rate: up to 100 drops/min = 300 ml/h.

Method of administration

Intravenous use

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Impairment of lactate utilisation with hyperlactataemia (see also section 4.4)
- Hyperhydration
- Circulatory overload
- Congestive heart failure
- Hypertension
- Impaired renal function
- Sever liver damage
- Oedema with sodium retention
- Respiratory alkalosis

This solution is not indicated for the treatment of severe metabolic acidosis.

4.4 Special warnings and precautions for use

This solution should only be administered with particular caution in the following conditions:
- hypertonic dehydration
- hyperkalaemia
- hypernatraemia
- hyperchloraemia
- hypercalcaemia

High volume infusions must only be used under specific monitoring in patients with cardiac or pulmonary failure, lung or brain oedema 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.
.
Lactate utilisation may be impaired in the presence of hypoxia or hepatic insufficiency.

Compound sodium lactate contains an amount of potassium that is similar to that of the physiological concentration of potassium in human blood. Nevertheless it is not suitable for the treatment of patients with severe potassium deficiency.

As the solution contains metabolisable ions (e.g. lactate) it may cause metabolic alkalosis. Therefore the solution has to be administered with caution in patients with metabolic alkalosis.

Solutions containing sodium chloride should be administered with caution to patients with

- cardiac insufficiency or peripheral oedema,
- present or imminent eclampsia, aldosteronism or other conditions or treatment (e. g. corticoids/steroids) associated with sodium retention (see also section 4.5).

Solutions containing potassium salts should be administered with caution to patients with cardiac disease, conditions predisposing to hyperkalaemia such as adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns.
Because of the presence of calcium:

- Care should be taken to prevent extravasation during intravenous infusion.
- The solution should be given cautiously to patients withdiseases associated with elevated vitamin D concentrations such as sarcoidosis. Thus administration of calcium containing solutions should be avoided in patients with nephroliths or with a history of nephroliths.
- In case of concomitant blood transfusion, the solution must not be administered via the same in-fusion set.

Patients with chronic hyponatraemia:
Too rapid correction of serum sodium levels must be avoided in patients with chronic hyponatraemia as rapid increases of serum sodium levels may in rare cases lead to osmotic adverse effects, e.g. the osmotic demyelinisation syndrome.

<u>Paediatric patients</u>
The solution should be administered only with special care to newborns younger than 3 months.

Clinical monitoring should include checks of serum electrolyte levels, acid-base balance and water balance.

Serum lactate should be monitored carefully and if lactate accumulates during infusion, the dosage and infusion rate should be reduced or administration of the solution should eventually be discontinued.

In case of pressure infusion, which may be necessary in vital emergencies, all air must be removed from the plastic container and the infusion set before the solution is administered.

4.5 Interaction with other medicinal products and other forms of interaction

Administration of Compound Sodium Lactate in accordance with the recommended indications and contraindications does not increase the plasma concentrations of the electrolytes contained in it. In case there is a rise of any electrolyte's concentration due to other reasons the following interactions should be considered.

- Related to sodium

Corticoids/steroids and carbenoxolone may be associated with the retention of sodium and water (with oedema and hypertension).

- Related to potassium

Suxamethonium, potassium-sparing diuretics (amilorid, spironolactone, triamteren, alone or in association), ACE inhibitors (e.g. captopril, enalapril), Angiotensin II receptor antagonists (e.g. valsartan, losartan), tacrolimus, cyclosporine may increase the concentration of potassium in the plasma and lead to potentially fatal hyperkalaemia notably in case of renal failure increasing the hyperkalaemic effect.

- Related to calcium

- Digitalis glycosides (cardiac glycosides) may undergo enhancement of their effects during hypercalcaemia and lead to serious or fatal cardiac arrhythmia.
- Thiazid-diuretics and Vitamin D administered simultaneously with calcium may induce hypercalcaemia.

- If bisphosphonates, fluorides, several fluorchinolones and tetracyclines are administered simultaneously with calcium containing solutions the bioavailablility (reduced absorption) of above named medicinal products may be reduced.

- Related to lactate

The administration of bicarbonate or bicarbonate precursor like lactate leads to alkalini-sation of the urine with increased renal clearance of acidic drugs (e.g. salicylic acid). The half life of basic medicinal products – especially sympathomimetics (e.g. ephedrine, pseudoephedrine) and stimulants (e.g. dexamphetaminesulphate, fenfluramine hydrochloride) will be prolonged if lactate containing solutions are administered simultaneously.

- 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of the components of Compound Sodium Lactate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As all components of Compound Sodium Lactate are naturally present in the body and their bio-chemical properties are well known the product can be used as indicated.
Compound Sodium Lactate 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).
Caution should be exercised in toxaemia of pregnancy.

Breast-feeding

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

Fertility
No special precautions.

4.7 Effects on ability to drive and use machines

This medicinal product has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed according to their frequencies as follows:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

Metabolism and nutrition disorders:
Not known: Hospital Acquired Hyponatraemia*

Neurological disorders:
Not known: Hyponatraemic encephalopathy*

* Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy (see sections 4.2 and 4.4).

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

Symptoms

Overdose may result in hyperhydration with increased skin tension, venous congestion, oedema - possibly also lung or brain oedema -, electrolyte and acid-base imbalances as well as serum hyperosmolarity.

Treatment

Cessation of infusion, administration of diuretics with continuous monitoring of serum electrolytes, correction of electrolyte and acid-base imbalances.
In severe cases of overdose dialysis may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Solutions affecting the electrolyte balance, electrolytes
ATC-Code: B05B B01

Mechanism of action
The solution contains the essential ions present in extracellular fluid. Therefore the pharmacodynamic properties of the ions contained in it (sodium, potassium, calcium, chloride, lactate) are the same as in normal physiology.

Lactate is a key substrate in intermediary metabolism. *Inter alia*, it is oxidised to bicarbonate, exerting a mild alkalinising effect.

Pharmacodynamic effect
Compound Sodium Lactate has a similar electrolyte composition as the extracellular fluid (neglecting some very minor differences). It is used for correction of serum electrolyte and acid-base imbalances. Electrolytes are administered in order to achieve or to maintain a normal osmotic situation in both the extra- and the intracellular space.

Due to its distribution (see below) the solution has a short haemodynamic effect.

On account of the proportion of metabolisable anions Compound Sodium Lactate is particularly indicated in patients with a tendency to acidosis.

5.2 Pharmacokinetic properties

Absorption
Since the ingredients of Compound Sodium Lactate are infused intravenously their bioavailability is 100 %.

Distribution
Administration of Compound Sodium Lactate directly results in replenishment of the interstitial space which amounts to about $^{2}/_{3}$ of the extracellular space. Only $^{1}/_{3}$ of the administered volume stays in the intravascular space. Thus the solution has a short haemodynamic effect.

Biotransformation, elimination
Potassium, sodium, and chloride are mainly excreted in urine but small amounts are lost via the skin and also the intestinal tract. Especially surgery results in increased urinary excretion of potassium while water and sodium is retained.

Calcium is mainly excreted via the functioning kidneys. Small amounts are lost via the skin, hair, and nails. Calcium passes the placenta and is excreted into breast-milk.

Lactate is converted to bicarbonate and CO_2, both are normal body constituents. Plasma concentrations of bicarbonate and lactate are regulated by the kidneys and the plasma concentration of CO_2 is regulated by the lung. Lactate metabolism is impaired in states of hypoxia and in liver insufficiency.

5.3 Preclinical safety data

Non-clinical data for the individual components of Compound Sodium Lactate reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

Incompatibility has been reported with novobiocin sodium, oxytetracycline hydrochloride, sodium bicarbonate, sodium calcium edetate, and sulphadiazine sodium.

Medicinal products containing oxalate, phosphate, or carbonate/bicarbonate may cause precipitation upon mixing with Compound Sodium Lactate.

No other medicinal product or substance should be added to the fluid unless known to be compatible.

6.3 Shelf life

- unopened
The expiry date of the product is indicated on the packaging materials.

- after first opening
Not applicable, see section 6.6

- after admixture of additives
From the 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 dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

For storage conditions after admixture of additives to medicinal product, see section 6.3.

6.5 Nature and contents of container

- Bottles of low-density polyethylene (LD-PE), contents: 500 ml, 1000 ml available in packs of 10 × 500 ml, 10 × 1000 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Only to be used if solution is clear, colourless and the container and its closure do not show visible signs of damage.

Containers are for single-use. Discard container and any unused content after use.
Do not reconnect partially used containers.

7 MANUFACTURER

B. Braun Melsungen AG.,
Carl-Braun-Straße 1
D-34212 Melsungen, Germany

8 REGISTRATION HOLDER

Lapidot Medical Import and Marketing Ltd.
8 Hashita Street, Industrial Park Caesarea 38900, ISRAEL

9 MARKETING AUTHORISATION NUMBER

117-58-27994-12

Revised in September 2023 according to MOH guidelines