Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hartmann's SolutionCompound Sodium Lactate Intravenous Infusion BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1000 ml contains :

Sodium Chloride	6.00 g
Potassium Chloride	0.40 g
Calcium Chloride dihydrate	0.27 g
Sodium lactate 60%	5.16 g

ionic forumla

Sodium (Na^+)	131 mmol/l
Potassium (K^+)	5 mmol/l
Calcium (Ca^{++})	2 mmol/l
Chloride (Cl^-)	111 mmol/l
Bicarbonate (as Lactate)	29 mmol/l

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear colourless solution.

Osmolarity : 278 mOsm/l (approx.)
pH : 5.0 – 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ringer Lactate solution is indicated for :
- Restoration of extracellular fluid and electrolyte 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 hypovolemia 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
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 litres / 24h
- for paediatric patients: 20 ml to 100 ml/kg/24 h.

Special clinical conditions, such as massive blood loss, burns, surgical drains, diarrhea, require additional adjustments of the necessary IV fluid volume.

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.

Administration rate:
The infusion rate is usually 40 ml/kg/24h in adults.
In pediatric patients the infusion rate is 5 ml/kg/h in 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 school children. In children with burns, the dose is on average 3.4 ml/kg/percent 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: age ranges from about 28 days to 23 months (a toddler is an infant who can walk)
- Children and School children: age ranges from about 2 years to 11 years

Method of administration:
The administration is performed by intravenous route using sterile and non-pyrogenic equipment.
Hartmann's Solution tonicity: slightly hypotonic.
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).

4.3 Contraindications

Do not administer in case of:
- Extracellular hyperhydration or hypervolemia
- Severe renal insufficiency (with oliguria/anuria)
- Uncompensated cardiac failure
- Hyperkalaemia
- Hypernatraemia
- Hypercalcaemia
- Hyperchloraemia
- Metabolic alkalosis
- Severe metabolic acidosis
- Lactic acidosis
- Severe hepatocellular insufficiency or impaired lactate metabolism
- General oedema and ascitic cirrhosis
- Concomitant digitalis therapy and treatment with potassium-sparing diuretics (see section 4.5)

4.4 Special warnings and precautions for use

The patient's clinical status and laboratory parameters (blood and urine electrolytes as well as acid-base balance) must be monitored during use of this solution. The plasma potassium level of the patient must be particularly closely monitored in patients at risk of hyperkalaemia.

Solutions containing sodium chloride should be carefully administered to patients with hypertension, heart failure, peripheral or pulmonary oedema, impaired renal function, pre-eclampsia, aldosteronism, or other conditions associated with sodium retention (see also section 4.5).

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.

Although Ringer 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.

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 given cautiously to patients with impaired renal function, or disease associated with elevated vitamin D concentrations such as sarcoidosis. They should be avoided in patients with calcium renal calculi, or a history of renal calculi. In case of concomitant blood transfusion and because of the presence of calcium, Ringer lactate solution must not be administered via the same infusion system because of the risk of coagulation.

Ringer lactate solution may cause metabolic alkalosis because of the presence of lactate ions.

Ringer lactate solution may not produce its alkalinizing action in patients with liver insufficiency since lactate metabolism may be impaired.

The solution containing lactate should be administered with particular care to neonates less than 3 months old.

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

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.

4.5 Interaction with other medicinal products and other forms of interactions

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.

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

Interactions associated with calcium:
- Infusion in association with digitalis cardiac glycosides is contra-indicated because of the risk of severe to fatal cardiac arrhythmia particularly in the case of hypokalaemia
- Care should be taken in the concurrent use of thiazide diuretics or vitamin D because of the risk of hypercalcaemia resulting from reduced urinary clearance of calcium.
- Bisphosphonates, fluoride, some fluoroquinolones and tetracyclines which are less absorbed (lower availability) when administered with calcium.

Interactions associated with potassium:
- Care should be taken in concurrent use of drugs containing potassium and drugs which have the potential for inducing hyperkalaemia, such as potassium-sparing diuretics given alone or in combination (such as spironolactone, triamterene, amiloride, potassium canrenoate), ACE inhibitors, angiotensin-II receptor antagonists, tacrolimus and ciclosporin.

Interaction associated with lactate (which is metabolized into bicarbonate):
- Acidic drugs such as salicylates, barbiturates and lithium whose renal clearance is increased because of the alkalinisation of urine by the bicarbonate resulting from lactate metabolism.
- Alkaline drugs, notably sympathomimetics (e.g. ephedrine, pseudoephedrine) and stimulants (e.g. dexamphetamine sulphate, phenfluramine hydrochloride) whose half-life is prolonged (slowest elimination).

4.6 Fertility, pregnancy and lactation

Ringer Lactate solution can be used safely during pregnancy and lactation as long as the electrolyte- and fluid balance is controlled.

Hartmann'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 sections 4.4, 4.5 and 4.8).

It is reminded that calcium crosses the placenta and is distributed into breast milk.

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

Not applicable.

4.8 Undesirable effects

During administration of Ringer Lactate solution, the following undesirable effects have been reported as:
- very common:
Allergic reactions or anaphylactic/anaphylactoid symptoms such as localized or generalized urticaria, skin rash & erythema and itching/pruritus; skin swelling, periobial facial and/or laryngeal oedema (Quincke's oedema).
Nasal congestion, coughing, sneezing, bronchospasm and/or difficulty breathing.

- common:
Chest tightness, chest pain, with tachycardia or bradycardia.

Pruritus has been reported to occur in about 10% of patients receiving Ringer Lactate.

Hyperhydration and heart failure are very common in patients with cardiac disorder or pulmonary oedema.

Electrolytes disturbances have been very commonly reported too.

Lactate infusions commonly induce feelings of anxiety, and a few cases of panic attack have been reported.

- frequency unkown :
Hospital acquired hyponatraemia*
Acute hyponatraemic encephalopathy*
*Hospital acquired hyponatraemia may cause irreversible brain injury and death, due to development of acute hyponatraemic encephalopathy (see sections 4.2, 4.4 and 4.5).

Seizure may be precipitated by the alkalosis induced by lactate but this is uncommon.

Adverse reactions may be associated with 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, extravasation, and hypervolemia.

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the 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

Overuse 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 paraesthesia 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 hypercalcemia 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 hypercalcemia as well as to chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalcemia 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, haemodialysis, calcitonin, bisphosphonates, trisodium edetate) is required.

Excessive administration of sodium lactate may lead to hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Symptoms may include mood changes, tiredness, shortness of breath, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop especially in hypocalcemic patients. Treatment of metabolic alkalosis associated with 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: plasma substitutes and infusion solutions / electrolytes, ATC code: B05BB01 (B: blood and haemopoietic organs)

Ringer Lactate solution is an isotonic solution of electrolytes. The constituents of Ringer Lactate and their concentrations are designed to match those of plasma.

The pharmacodynamic properties of the solution are those of its constituents (sodium, potassium, calcium and chloride).

The main effect of 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 Ringer Lactate, central venous pressure changes were associated with a secretion of atrial natriuretic peptide.

In healthy volunteers, 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 Ringer Lactate.

When medication is added to 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 Ringer Lactate solution are those of the ions its composition includes (sodium, potassium, calcium and chloride).

Infusion of Ringer Lactate in normal hemodynamically stable adults does not increase circulating lactate concentrations.

The lactate in 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 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Use immediately on removal from overwrap.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original outer container in order to protect from light.

6.5 Nature and contents of container

- Flexible DEHP-plasticized PVC Macoflex bags containing 250 ml, 500 ml or 1000 ml solution, individually overwrapped in transparent polypropylene laminate.
- Flexible polyolefin (ethylene-propylene copolymer) Macoflex *N* bags containing 250 ml, 500 ml or 1000 ml solution, individually overwrapped in transparent polypropylene laminate.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
Solution containing visible solid particles should not be used.
Do not use unless the solution is clear and the container undamaged.
Do not connect in series and purge the infusion system to remove all air because of the risk of air embolism.
Discard any unused solution.
Verify the integrity of the container and the site for attachment.
For slow infusion only.

Macoflex bags:
Remove the bag from the plastic overwrapping.
Remove the twist-off protector of the infusion site.
Connect to the administration set.

Addition of medicinal products:
The healthcare professional should assess compatibility by checking absence of colour change or formation of precipitate, insoluble complexes or crystals. Mix thoroughly with the solution. Use immediately after addition of medicine.

7 MARKETING AUTHORISATION HOLDER

MACO PHARMA
Rue Lorthiois
59420 Mouvaux
France

8 MARKETING AUTHORISATION NUMBER

PA22638/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th May 2007
Date of last renewal: 27th September 2010

10 DATE OF REVISION OF THE TEXT

March 2019