IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0167/063/005
Case No: 2069237

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Baxter Healthcare Limited

Caxton Way, **Thetford**, **Norfolk IP24 3SE**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Compound Sodium Lactate & Glucose 5% w/v Solution for Infusion.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/03/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Compound Sodium Lactate & Glucose 5% w/v Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glucose (as monohydrate)	50.0 g/l
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

200 kcal/L (840 kJ/L)

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear solution, free from visible particles.
555 mOsm/l (approx). pH: 4.0 – 6.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Compound Sodium Lactate & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v solution) is used in the following indications when a source of carbohydrate is required

- 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 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

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 & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v 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 babies and children :
- 0-10 kg body weight : 100 ml / kg / 24 h
- 10-20 kg body weight: 1000 ml + (50 ml/ kg over 10 kg) / 24h
- > 20 kg body weight : 1500 ml +(20 ml/ kg over 20 kg) / 24h.".

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 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
The infusion rate should not exceed the patient's glucose oxidation capacities in order to avoid hyperglycaemia. Therefore the maximum acute administration rate ranges from 5mg/kg/min for adults to 10-18 mg/kg/min for babies and children, depending on the age and the total body mass.

Note:
- infants and toddlers: age ranges from about 28 days to 23 months (a toddler is an infant who can walk)
- Children and Schoolchildren: 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

The solution is contra-indicated in patients presenting:

- Extracellular hyperhydration or hypervolemia
- Severe renal insufficiency (with oliguria/anuria)
- Uncompensated cardiac failure
- Hyperkalemia
- Hypernatremia
- Hypercalcaemia
- Hyperchloremia
- Metabolic alkalosis
- Severe metabolic acidosis.
- Lactic acidosis.
- Severe hepatocellular insufficiency or impaired lactate metabolism
- General oedema and ascitic cirrhosis
- Concomitant digitalis therapy (*see section 4.5 "Interactions with other medicinal products and other forms of interaction")*

The solution is also contraindicated in case of uncompensated diabetes, other known glucose intolerances (such as metabolic stress situations), hyperosmolar coma, hyperglycaemia, hyperlactatemia.

4.4 Special warnings and precautions for use

Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v) solution is an hypertonic solution, with an approximate osmolarity of 555 mOsm/l
High volume infusion must be used under specific monitoring in patients with cardiac or pulmonary failure.

The patient's clinical status and laboratory parameters (electrolytes and glucose levels in blood and urine 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 edema, impaired renal function, pre-eclampsia, aldosteronism, or other conditions 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.
Although Compound Sodium Lactate & Glucose 5% solution (Ringer Lactate & Glucose 5% 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 take 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, Compound Sodium Lactate & Glucose 5% w/v solution (Ringer lactate & Glucose 5% w/v solution) must not be administered via the same infusion system because of the risk of coagulation.
Infusion of Compound Sodium Lactate & Glucose 5% w/v (Ringer lactate & Glucose 5% w/v) solution may cause metabolic alkalosis because of the presence of lactate ions.
Compound Sodium Lactate & Glucose 5% w/v 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.
Due to glucose presence, Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v) should not be infused concomitantly to massive blood transfusion (risk of pseudo-agglutination) through the same infusion set.
Administration of glucose containing solutions may lead to hyperglycaemia. In this case, it is recommended not to use this solution after acute ischemic strokes as hyperglycemia has been implicated in increasing cerebral ischemic brain damage and impairing recovery. Infusion of glucose solution could be contraindicated in the first 24 hours following head trauma and blood glucose concentration should be closely monitored during intracranial hypertension episodes. If hyperglycaemia occurs, rate of infusion should be adjusted or insulin administered.

In diabetic patients, the amount of infused glucose has to be taken into account and insulin requirements may be modified

4.5 Interaction with other medicinal products and other forms of interaction

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 hyperkalemia notably in case of a renal failure increasing the hyperkalemic effect

Interaction related to the presence of calcium:

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

- 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):

- 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 Pregnancy and lactation

Compound Sodium Lactate & Glucose 5% w/v Solution for Infusion (Ringer Lactate & Glucose 5% w/v solution for infusion) 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.

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 Lactated ringer’s & Glucose 5% injection, USP, 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/pruritis; skin swelling, periobial facial and/or laryngeal edema (Quincke's edema).

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 Compound Sodium Lactate (Ringer Lactate).

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

Electrolytes disturbances have been very commonly reported too.

Lactate infusions commonly induce feeling of anxiety, and few cases of panic attack have been reported

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

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, 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.

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 hyperkalemia, 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 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, hemodialysis, calcitonin, bisphosphonates, trisodium edetate) is required.

Excessive administration of sodium lactate may lead to hypokalemia 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.

Prolonged administration or rapid infusion of large volumes of glucose containing solution may lead to hyperosmolarity, dehydration, hyperglycaemia, hyperglucosuria and osmotic dieresis (due to hyperglycaemia).

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): B05BB02 “Electrolytes with Carbohydrates”.

Compound Sodium Lactate & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v solution) is an hypertonic solution of electrolytes and glucose.

The pharmacological properties of the Compound Sodium Lactate & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v solution) are those of its components (glucose, sodium, potassium, calcium, chloride and lactate).

Glucose is the main source of energy, and this solution provides 200 kcal/L.

The main effect of Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v) 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.

There is no significant changes in glucagon, norepinephrine, epinephrine, blood glucose and insulin levels in aortic surgery patients receiving Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v).

When medication is added to Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v), 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 & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v solution) are those of its components (glucose, sodium, potassium, calcium, chloride and lactate).

Infusion of Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v) 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 & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v 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 & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v), 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 & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v) 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

As with all parenteral solutions, before adding medications, compatibility of these additives with the solution in Viaflo container must be assessed.

It is the responsibility of the physician to judge the incompatibility of an additive medication with the Compound Sodium Lactate & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v solution) by checking for eventual color change and/or eventual precipitate, insoluble complexes or crystals apparition. The Instructions for Use of the medication to be added must be consulted.

Before adding a drug, verify it is soluble and stable in water at the pH of Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v) (pH 4.0 to 6.5).

When a compatible medication is added to the Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v), the solution must be administered immediately.

As a guidance the following medications are incompatible with the Compound Sodium Lactate & Glucose 5% w/v solution (Ringer Lactate & Glucose 5% w/v solution) (***non-exhaustive listing***):

Medications incompatible with Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v)

- Aminocaproic acid (Amicar®)
- Amphotericin B
- Cortisone acetate (Cortone acetate®)

- Diethylstilbestrol
- Etamivan (Emivan®)
- Ethyl alcohol
- Phosphate and carbonate solutions
- Oxytetracycline (Terramycyn®)
- Thiopental sodium
- Versenate disodium

Medications with partial incompatibility with Compound Sodium Lactate & Glucose 5% w/v (Ringer Lactate & Glucose 5% w/v):

- Tetracycline (Achromycin®) stable for 12 hours
- Ampicillin sodium

concentration of 2%-3% stable for 4 hours
concentration >3% must be given within 1 hour

- Minocycline (Minocin®) stable for 12 hours
- Doxycycline (Vibramycin®) stable for 6 hours

Those additives known to be incompatible should not be used.

6.3 Shelf Life

Shelf-life (Unopened): 30 months for 1000ml container.
2 years for 250ml and 500ml container.

In-use shelf-life: Additives

Chemical and Physical stability of any additive at the pH of Compound Sodium Lactate & Glucose 5% w/v solution (Ringer Lactate and Glucose 5% w/v 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

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 (PL 2442).

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

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

Outer carton contents:	*30*	bags of	250ml
	20	bags of	500ml
	10	bags of	1000ml

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

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 over wrap 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.

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.
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.

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

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

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

2. Preparation for administration
Use sterile material for preparation and administration.
a. Suspend container from eyelet support.
b. 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.
c. Use an aseptic method to set up the infusion.
d. Attach administration set. Refer to complete directions accompanying set for connection, priming of the set and administration of the solution.

3. Techniques for injection of additive medications

Warning: Additives may be incompatible.

To add medication before administration
a. Disinfect medication site.
b. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
c. 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
a. Close clamp on the set.
b. Disinfect medication site.
c. Using syringe with 19 to 22 gauge needle, puncture resealable medication port and inject.
d. Remove container from IV pole and/or turn to an upright position.
e. Evacuate both ports by tapping gently while the container is in an upright position.
f. Mix solution and medication thoroughly.
g. Return container to in use position, re-open the clamp and continue administration.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
Caxton Way, Thetford
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0167/063/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 April 2003

Date of last renewal: 19 March 2006

10 DATE OF REVISION OF THE TEXT

December 2009