SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Plasma-Lyte® 148 (pH 7.4) solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium Chloride: ..... 5.26 g/l
Potassium Chloride: ..... 0.37 g/l
Magnesium Chloride hexahydrate: ..... 0.30 g/l
Sodium Acetate trihydrate: ..... 3.68 g/l
Sodium Gluconate: ..... 5.02 g/l

	Na^+	K^+	Mg^{++}	Cl^-	CH_3COO^- (Acetate)	$C_6H_{11}O_7^-$ (Gluconate)
mmol/l	140	5.0	1.5	98	27	23
mEq/l	140	5.0	3.0	98	27	23

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear solution, free from visible particles

Osmolarity: 295 mOsm/l (approx.)
pH: approx. 7.4 (6.5 to 8.0)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Plasma-Lyte 148 (pH 7.4) is indicated:

- for fluid replacement (e.g. after burns, head injury, fracture, infection, and peritoneal irritation),
- as intraoperative fluid replacement,
- in haemorrhagic shock and clinical conditions requiring rapid blood transfusions (compatibility with blood),
- in mild to moderate metabolic acidosis, also in case of lactate metabolism impairment.

4.2 Posology and method of administration

Posology:

Adults, older patients and adolescents (age 12 years and over):
Fluid balance, serum electrolytes and acid-base balance should 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.
Plasma-Lyte 148 (pH 7.4) solution has a tonicity of 295 mOsm/l (approx.).

The infusion rate and volume depend on the age, weight, clinical condition (e.g. burns, surgery, head-injury, infections), and concomitant therapy and concomitant therapy should be determined by the consulting physician experienced in intravenous fluid therapy (see sections 4.4. and 4.8).

The recommended dosage is: 500 ml to 3 litres / 24 h.

Administration rate:

The infusion rate is usually 40 mL/kg/24h in adults, the elderly and adolescents.

When used for intraoperative fluid replacement, normal rate can be higher and is about 15 mL/kg/h.

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.

Paediatric population

Safety and effectiveness of Plasma-Lyte 148 (pH 7.4) in children have not been established by adequate and well controlled trials. Treatment of paediatric patients is described in literature.
The dosage varies with weight:

- 0-10 kg body weight: up to 100 ml/kg/24h
- 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.

The administration rate varies with weight:

- 0-10 kg body weight: 6-8 ml/kg/h
- 10-20 kg body weight: 4-6 ml/kg/h
- > 20 kg body weight: 2-4 ml/kg/h

Method of administration:

The administration is performed by intravenous route.

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. This solution can be administered before, during or after a blood transfusion.

Due to its iso-osmolality, this solution can be administered through a peripheral vein.

The solution should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless the solution is clear 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 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. Pressurizing intravenous solutions contained in flexible plastics 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

4.3 Contraindications

The solution is contra-indicated in patients presenting:

- Hyperkalaemia
- Renal failure
- Heart block
- Metabolic or respiratory alkalosis
- Hypochlorhydria
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

WARNINGS
Electrolyte balance
Plasma-Lyte 148 (pH 7.4) is not indicated for the treatment of hypochloraemic hypokalaemic alkalosis.

Plasma-Lyte 148 (pH 7.4) is not indicated for the primary treatment of severe metabolic acidosis neither for the treatment of hypomagnesaemia.

Use in Patients with or at Risk for and from Hypermagnaesemia
Parenteral magnesium salts should be used with caution in less severe degrees of renal impairment and in patients with myasthenia gravis. Patients should be monitored for clinical signs of excess magnesium, particularly when being treated for eclampsia. (See also section 4.5 – Interactions with other Medicinal Products and other forms of interaction)

Use in patients with Hypocalcaemia
Plasma-Lyte 148 (pH 7.4) contains no calcium, and an increase in plasma pH due to its alkalinizing effect may lower the concentration of ionized (not protein-bound) calcium. Plasma-Lyte 148 (pH 7.4) should be administered with particular caution to patients with hypocalcaemia.

Use in Patients with or at Risk for Hyperkalaemia

Solutions containing potassium salts should be administered with caution to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. The plasma potassium level of the patient should be particularly closely monitored in patients at risk of hyperkalaemia.

The following combinations are not recommended; they increase the concentration of potassium in the plasma and may lead to potentially fatal hyperkalaemia notably in case of renal failure increasing the hyperkalaemic effects (see 4.5).

- Concomitant use with potassium-sparing diuretics (amiloride, potassium canreonate, spironolactone, triamterene)
- Angiotensin converting enzyme inhibitors (ACEi) and, by extrapolation, angiotensin II receptor antagonists : hyperkalaemia potentially lethal
- Tacrolimus, cyclosporin

Use in patients with potassium deficiency
Although Plasma-Lyte 148 (pH 7.4) solution has a potassium concentration similar to the concentration in plasma, it is insufficient to produce a useful effect in case of severe potassium deficiency and therefore it should not be used for this purpose.

Fluid balance/renal function.
Risk of Fluid and/or Solute Overload and Electrolyte Disturbances

The patient's clinical status and laboratory parameters (fluid balance, blood and urine electrolytes as well as acid-base balance) must be monitored during use of this solution. Depending on the volume and rate of infusion, intravenous administration of Plasma-Lyte 148 (pH 7.4) can cause
− fluid and/or solute overload resulting in overhydration/hypervolaemia therefore high volume infusion must be used under specific monitoring in patients with cardiac, pulmonary or renal failure.
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 or Overhydration, or Conditions that Cause Sodium Retention and Oedema

Plasma-Lyte 148 (pH 7.4) should be administered with particular caution to hypervolaemic or overhydrated patients.

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 forms of interaction).

Use in Patients with Severe Renal Impairment

Plasma-Lyte 148 (pH 7.4) should be administered with particular caution to patients with severe renal impairment. In such patients administration of Plasma-Lyte 148 (pH 7.4) may result in sodium and/or potassium or magnesium retention.

Acid-base balance

Use in Patients with or at Risk for Alkalosis

Plasma-Lyte 148 (pH 7.4) should be administered with particular caution to patients with alkalosis or at risk for alkalosis. Excess administration of Plasma-Lyte 148 (pH 7.4) can result in metabolic alkalosis because of the presence of acetate and gluconate ions.

Other warnings

Hypersensitivity Reactions

Hypersensitivity/infusion reactions, including anaphylactoid reactions, have been reported with Plasma-Lyte 148 (pH 7.4).

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.

Administration

Administration in the postoperative period shortly after recovery from neuromuscular block should be used with caution since magnesium salts can lead to recurarisation effect.

When used concomitantly with parenteral nutrition, electrolyte supply should be taken into account and adjusted accordingly.

PRECAUTIONS

Interference with laboratory tests for gluconate containing solutions
There have been reports of false-positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving Baxter gluconate containing Plasmalyte solutions. These patients were subsequently found to be free of *Aspergillus* infection. Therefore, positive test results for this test in patients receiving Baxter gluconate containing Plasmalyte solutions should be interpreted cautiously and confirmed by other diagnostic methods.

Administration

Adding other medications or using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In case of an adverse reaction, infusion must be stopped immediately.
For information on incompatibilities and preparation of the product and additives, please see section 6.2 and 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

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:

- 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:

The following combinations increase the concentration of potassium in the plasma and may lead to potentially fatal hyperkalaemia notably in case of renal failure increasing the hyperkalaemic effects:

- Potassium-sparing diuretics (amiloride, potassium canreonate, spironolactone, triamterene, alone or in combination) (see 4.4),
- Angiotensin converting enzyme inhibitors (ACEi) and, by extrapolation, angiotensin II receptor antagonists: hyperkalaemia potentially lethal (see 4.4),

Tacrolimus, cyclosporin (see 4.4)

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 magnesium:

Neuromuscular blockers such as tubocurarine, suxamethonium, and vecuronium whose effects are enhanced by the presence of magnesium.
Acetylcholine whose release and effects are reduced by magnesium salts what may contribute to neuromuscular blockade.
Aminoglycoside antibacterials and nifedipine that have additive effects with parenteral magnesium and enhanced the neuromuscular blocking.

Interaction related to the presence of acetate and gluconate (which are metabolised into bicarbonate):

Caution is advised when administering Plasma-Lyte 148 (pH 7.4) to patients treated with drugs for which renal elimination is pH dependent. Due to its alkalinizing effect (formation of bicarbonate), Plasma-Lyte 148 (pH 7.4) 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 acetate and gluconate metabolism.
Renal clearance of alkaline drugs such as sympathomimetics (e.g. ephedrine, pseudoephedrine) and stimulants (e.g. dexamphetamine sulphate, phenfluramine hydrochloride) may be decreased.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation
There are no adequate data from the use of Plasma-Lyte 148 (pH 7.4) solution for infusion in pregnant or lactating women. The potential risks and benefits for each specific patient should be carefully considered before using Plasma-Lyte 148 (pH 7.4) solution for infusion in pregnancy or lactating woman.

Plasma-Lyte® 148 (pH 7.4) 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).

Fertility
There is no information on the effects Plasma-Lyte 148 (pH 7.4) solution for infusion on fertility.

4.7 Effects on ability to drive and use machines

There is no information of the effects of Plasma-Lyte 148 (pH 7.4) solution for infusion on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse reactions have been reported in the post-marketing experience, with various electrolyte solutions similar to Plasma-lyte, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

Frequency is defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100): rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); and not known (cannot be estimated from the available data)

System Organ Class (SOC)	*MedDRA Preferred Term*	*Frequency*

Immune system disorders	Hypersensitivity/infusion reaction (including Anaphylactoid reaction, and the following manifestations: Tachycardia, Palpitations, Chest pain, Chest discomfort, Dyspnea, Respiratory rate increased, Flushing, Hyperaemia, Asthenia, Feeling abnormal, Piloerection, Oedema peripheral, Pyrexia Urticaria **Hypotension, Wheezing, Cold sweat, Chills, Hyperkalaemia)*	Not known
Metabolism and nutrition disorders	Hypervolaemia Hospital acquired hyponatraemia**	Not known
Nervous system disorders	Seizures Acute hyponatraemic encephalopathy**	Not known
Vascular disorders	Thrombophlebitis Venous thrombosis	Not known Not known
Skin and subcutaneous tissue disorders	Urticaria	Not known
General disorders and administration site conditions	Infusion site reactions (e.g., Burning sensation Fever Injection site pain Injection site reaction Injection site phlebitis Injection site irritation Injection site infection Extravasation)	Not known
Investigations	False positive laboratory results (Bio-Rad Laboratories' Platelia *Aspergillus* EIA test) (see Section 4.4)	Not known

* The adverse reactions highlighted in italic are reported for other similar products

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

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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

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 paresthesia of the extremities, muscle weakness, paralysis, cardiac arrhythmias, heart block, cardiac arrest, and mental confusion. Treatment of hyperkalaemia involves the administration of calcium, insulin (with glucose) sodium bicarbonate, exchange resins or dialysis.

Excessive parenteral administration of magnesium salts leads to the developments of hypermagnesaemia, important signs of which are loss of deep tendon reflexes and respiratory depression, both due to neuromuscular blockade. Other symptoms of hypermagnesaemia may include nausea, vomiting, flushing of the skin, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, muscle weakness, bradycardia, coma, and cardiac arrest. A patient with supralethal hypermagnesaemia was successfully treated using assisted ventilation, calcium chloride, administered intravenously, and forced diuresis with mannitol infusions.

Excessive administration of chloride salts may cause a loss of bicarbonate with an acidifying effect.

Excessive administration of compounds, such as sodium acetate and sodium gluconate, which are metabolised to form the bicarbonate anion 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 hypocalcaemic patients. Treatment of metabolic alkalosis associated with bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance.

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: “Electrolytes” - ATC code: “B05BB01”

Plasma-Lyte 148 (pH 7.4) is an isotonic solution of electrolytes. The electrolytes constituents of Plasma-Lyte 148 (pH 7.4) solution and their concentrations are designed to match those of plasma.

The pharmacological properties of Plasma-Lyte 148 (pH 7.4) solution are those of its components (water, sodium, potassium, magnesium, chloride, acetate and gluconate).

The main effect of Plasma-Lyte 148 (pH 7.4) is the expansion of the extracellular compartment including both the interstitial fluid and the intravascular fluid.

Sodium acetate and gluconate are bicarbonate-producing salts and as such are alkalinizing agents.

When medication is added to Plasma-Lyte 148 (pH 7.4), the overall pharmacodynamics of the solution will depend on the nature of the drug used.

5.2. Pharmacokinetic Properties

The pharmacokinetic properties of the Plasma-Lyte 148 (pH 7.4) solution are those of the ions its composition includes (sodium, potassium, magnesium, chloride, acetate and gluconate).

Acetates are metabolised by muscle and peripheral tissues to bicarbonate, without solicitation of the liver.

When medication is added to Plasma-Lyte 148 (pH 7.4), the overall pharmacokinetics of the solution will depend on the nature of the drug used.

5.3 Preclinical safety data

Preclinical safety data of Plasma-Lyte 148 (pH 7.4) solution for infusion 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

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Additives

When introducing additives to Plasma-Lyte 148 (pH 7.4), aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives.

Incompatibility of the medicinal product to be added with the solution in Viaflo container must be assessed before addition.

The Instructions for Use of the medicinal product to be added must be consulted.

Before adding a substance or medication, verify it is soluble and/or stable in water and that the pH range of Plasma-Lyte 148 (pH 7.4) is appropriate (pH 6.5 - 8.0). After addition, check for a possible colour change and/or the appearance of precipitates, insoluble complexes or crystals.

Those additives known to be incompatible should not be used.

6.3 Shelf life

Shelf life as packaged: *24 months for the 500 ml and 1000 ml containers.*

Shelf life after first opening: The product should be used immediately after opening.

In-use shelf-life after reconstitution with additives:

Chemical and Physical stability of any additive at the pH of Plasma-Lyte 148 (pH 7.4) solution in the Viaflo container should be established prior to use.
From a microbiological point of view, the diluted 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 reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

For storage conditions after reconstitution of additives with the medicinal product, see section 6.3.

6.5 Nature and contents of container

The bags are composed of polyolefin/polyamide co-extruded plastic (PL 2442). The bags are overwrapped with a protective plastic pouch composed of polyamide/polypropylene which serves only to provide physical protection to the bags.

The bag size is either 500 or 1000mL.

Outer carton contents:

- 1 bag of 500ml
- 20 bags of 500ml
- 1 bag of 1000ml
- 10 bags of 1000ml
- 12 bags of 1000 ml

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.

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 broken.
   c. Check the solution for clarity 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: Some additives may be incompatible
   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

a. Disinfect medication site.
b. Using syringe with 19 gauge (1.10 mm) to 22 gauge (0.70 mm) 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 gauge (1.10 mm) to 22 gauge (0.70 mm) 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
Norfolk IP24 3SE
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00116/0332

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/2009

10 DATE OF REVISION OF THE TEXT

15/12/2023