SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Physiomax

2. Qualitative and quantitative composition
Sodium Chloride……526 mg
Sodium Gluconate……..……502 mg
Sodium Acetate trihydrate……...368 mg
Potassium Chloride……..... ….....37 mg
Magnesium Chloride hexahydrate……..……...30 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Solution for Intravenous Infusion

Description: A clear and almost colorless to pale yellow solution, essentially free from visible particles.

4. Clinical particulars
4.1 Therapeutic indications

Physiomax 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.

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 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 Physiomax 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

<u>Method of administration:</u>
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
Physiomax is not indicated for the treatment of hypochloraemic hypokalaemic alkalosis. Physiomax 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
Physiomax contains no calcium, and an increase in plasma pH due to its alkalinizing effect may lower the concentration of ionized (not protein-bound) calcium. Physiomax 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 Physiomax 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 Physiomax 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
Physiomax 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
Physiomax should be administered with particular caution to patients with severe renal impairment. In such patient's administration of Physiomax may result in sodium and/or potassium or magnesium retention.

Acid-base balance
Use in Patients with or at Risk for Alkalosis
Physiomax should be administered with particular caution to patients with alkalosis or at risk for alkalosis. Excess administration of Physiomax 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 Physiomax.
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 Physiomax to patients treated with drugs for which renal elimination is pH dependent. Due to its alkalinizing effect (formation of bicarbonate), Physiomax 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 Physiomax solution for infusion in pregnant or lactating women. The potential risks and benefits for each specific patient should be carefully considered before using Physiomax solution for infusion in pregnancy or lactating woman. Physiomax 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).

Fertility

There is no information on the effects Physiomax solution for infusion on fertility.

4.7 Effects on ability to drive and use machines

There is no information of the effects of Physiomax 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 Physiomax, 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 providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

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”.
Physiomax is an isotonic solution of electrolytes. The electrolytes constituents of Physiomax solution and their concentrations are designed to match those of plasma. The pharmacological properties of Physiomax solution are those of its components (water, sodium, potassium, magnesium, chloride, acetate and gluconate).

The main effect of Physiomax 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 Physiomax the overall pharmacodynamics of the solution will depend on the nature of the drug used.

5.2 Pharmacokinetic properties
The pharmacokinetic properties of the Physiomax 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 Physiomax the overall pharmacokinetics of the solution will depend on the nature of the drug used.

5.3 Preclinical safety data
Preclinical safety data of Physiomax 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
Sodium Hydroxide (for pH adjustment)
Hydrochloric Acid (for pH adjustment)
Water for Injections (As vehicle)

6.2 Incompatibilities
Additives
When introducing additives to Physiomax 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 its 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 Physiomax 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*

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
It is available as 500 mL in Euro Head Plastic Bottle & Non-PVC Bag.

6.6 Special precautions for disposal and other handling
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.

7. Marketing authorisation holder
Otsuka Pharmaceutical India Private Limited
Survey No.199 to 201 & 208 to 210, Village – Vasana – Chacharwadi
Tal-Sanand, Dist: Ahmedabad – 382 213
India.

8. Marketing authorisation number(s)
TAN 20 HM 0420

9. Date of first authorisation/renewal of the authorisation
25/09/2020

10. Date of revision of the text