SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glucose 50% w/v Concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Anhydrous Glucose 50 %w/v equivalent to	500 g per 1000 ml
or	
Glucose Monohydrate	550 g per 1000 ml

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, slightly yellow solution.

Glucose 50% w/v has an osmolarity of 2775 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Glucose 50% w/v is for use in admixtures to provide temporary relief from the symptoms of increased intracranial pressure and hypoglycaemic coma and is also indicated for the supplementation of energy in parenteral nutrition.

4.2 Posology and method of administration

Posology

The dosage and rate of administration of Glucose 50% w/v are determined by several factors including the indication for use and the patient's age, weight and clinical condition.

Fluid balance, serum glucose, serum sodium and other electrolytes should be monitored before and during administration, especially 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 hyponatraemia.

Monitoring of serum sodium is particularly important for physiologically hypotonic fluids. Glucose 50% w/v may become extremely hypotonic after administration due to glucose metabolisation in the body (see sections 4.4, 4.5 and 4.8).

Method of administration

Glucose 50% w/v is for administration by intravenous infusion following appropriate dilution or incorporation in to a parenteral nutrition admixture.

Administration of hyperosmolar solutions may cause venous irritation and phlebitis.

The resultant admixture should be administered through a central or peripheral venous line depending on its final osmolarity. If the final mixture, to be administered, is hypertonic it may cause irritation of the vein when administered into a peripheral vein.

The infusion rate and volume depends on the age, weight, clinical and metabolic conditions of the patient, as well as concomitant therapy.

A gradual increase of flow rate should be considered when starting administration of glucose-containing products.

To reduce the risk of hypoglycaemia after discontinuation, a gradual decrease in flow rate before stopping the infusion should be considered.

Electrolyte supplementation may be indicated according to the clinical needs of the patient.

As indicated on an individual basis, vitamins and trace elements and other components (including amino acids and lipids) can be added to the parenteral regimen to meet nutrient needs and prevent deficiencies and complications from developing.

Dilute Glucose 50% w/v before use to a concentration which will, when administered with an amino acid (nitrogen) source, result in an appropriate calorie to gram of nitrogen ratio and which has an osmolarity consistent with the route of administration.

When Glucose 50% w/v is used in conjunction with amino acids, the rate of administration of glucose should not exceed 1g/kg/hour for optimal protein anabolism.

Use in Paediatric Patients

The infusion rate and volume depends on the age, weight, clinical and metabolic conditions of the patient, concomitant therapy and should be

determined by the consulting physician experienced in paediatric intravenous fluid therapy (see section 4.4).

4.3 Contraindications

Contra-indicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. See sections 4.4 and 4.8 for corn allergies
- Clinically significant hyperglycaemia

4.4 Special warnings and precautions for use

WARNINGS

Not for direct intravenous infusion. Must be appropriately diluted before use. The admixture obtained should be administered through a central or peripheral venous line depending on its final osmolarity.

Unless appropriately diluted infusion of hypertonic glucose solutions into a peripheral vein may result in vein irritation, vein damage, and thrombosis. Strongly hypertonic solutions should only be administered through an indwelling intravenous catheter with the tip located in a large vein such as the superior vena cava.

Prolonged intravenous infusion of this solution may cause thrombophlebitis extending from the site of infusion.

Dilution and other effects on serum electrolytes

Glucose intravenous infusions are usually isotonic solutions. In the body, however, glucose containing fluids can become extremely physiologically hypotonic due to rapid glucose metabolization (see section 4.2).

Depending on the tonicity of the solution, the volume and rate of infusion and depending on a patient's underlying clinical condition and capability to metabolize glucose, intravenous administration of glucose can cause:

- Hyperosmolality, osmotic diuresis and dehydration
- Hypoosmolality
- Electrolyte disturbances such as:
  - hypo- or hyperosmotic hyponatraemia (see below),
  - hypokalaemia,
  - hypophosphatemia,
  - hypomagnesaemia,
  - overhydration/hypervolemia and, for example, congested states, including pulmonary congestion and oedema.

The above effects do not only result from the administration of electrolyte-free fluid but also from glucose administration.

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 (brain oedema) characterized by headache, nausea, seizures, lethargy and vomiting. Patients with brain 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, and cerebral contusion) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

Hypoosmotic hyponatraemia can lead to headache, nausea, seizures, lethargy, coma, cerebral oedema, and death. Acute symptomatic hyponatraemic encephalopathy is considered a medical emergency.

The risk for developing hypoosmotic hyponatraemia is increased, for example,

- in children
- in elderly patients
- in women
- postoperatively
- in persons with psychogenic polydipsia

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

Particular caution is advised in patients at increased risk of water and electrolyte disturbances that could be aggravated by increased free water load, hyperglycaemia or possibly required insulin administration (see below).

Hyperglycaemia

As with the intravenous administration of nutrients (e.g., glucose, amino acids and lipids) in general, metabolic complications may occur if the nutrient intake is not adapted to the patient’s requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient’s needs.

Rapid administration of glucose solutions may produce substantial hyperglycaemia and a hyperosmolar syndrome.

To reduce the risk of hyperglycaemia-associated complications, the infusion rate must be adjusted and/or insulin administered.

Intravenous glucose should be administered with caution in patients with, for example:

- impaired glucose tolerance (such as in patients with renal failure or diabetes mellitus, or in the presence of sepsis, trauma, or shock),

- severe malnutrition (risk of precipitating a refeeding syndrome),
- thiamine deficiency, e.g., in patients with chronic alcoholism (risk of severe lactic acidosis due to impaired oxidative metabolisation of pyruvate),
- water and electrolyte disturbances that could be aggravated by increased glucose and/or free water load (see above).
- patients with ischemic stroke or severe traumatic brain injury
- avoid infusion within the first 24 hours following head trauma. Monitor blood glucose closely as early hyperglycaemia has been associated with poor outcomes in patients with severe traumatic brain injury.
- newborns (see below).

Effects on Insulin Secretion

Prolonged intravenous administration of glucose and associated hyperglycaemia may result in decreased rates of glucose-stimulated insulin secretion.

Hypersensitivity Reactions

Hypersensitivity/infusion reactions, including anaphylactic/anaphylactoid reactions, have been reported (see section 4.8).

Solutions containing glucose should be used with caution, if at all, in patients with known allergy to corn or corn products.

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.

Refeeding syndrome

Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications.

Liver disorders

Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition.

The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed early by a clinician

knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

Catheter infection and sepsis

Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral formulations, poor maintenance of catheters or contaminated solutions.

Immunosuppression and other factors such as hyperglycaemia, malnutrition and/or their underlying disease state may predispose patients to infectious complications.

Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device, and hyperglycaemia can help recognize early infections.

The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement, maintenance, as well as aseptic technique in nutritional formula preparation.

Precipitates

Pulmonary vascular precipitates have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution.

In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates.

If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated.

Paediatric population

The infusion rate and volume depends on the age, weight, clinical and metabolic conditions of the patient, concomitant therapy, and should be determined by a consulting physician experienced in paediatric intravenous fluid therapy.
In order to avoid potentially fatal over infusion of intravenous fluids to the neonate, special attention needs to be paid to the method of administration.

When using a syringe pump to administer intravenous fluids or medicines to neonates, a bag of fluid should not be left connected to the syringe.

When using an infusion pump all clamps on the intravenous administration set must be closed before removing the administration set from the pump, or switching the pump off. This is required regardless of whether the administration set has an anti-free flow device.
The intravenous infusion device and administration equipment must be frequently monitored.

Paediatric glycaemia related issues

Newborns, especially those born premature and with low birth weight - are at increased risk of developing hypo- or hyperglycaemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycaemic control in order to avoid potential long term adverse effects.
Hypoglycaemia in the newborn can cause prolonged seizures, coma and brain damage. Hyperglycaemia has been associated with intraventricular haemorrhage, late onset bacterial and fungal infection, retinopathy of prematurity, necrotizing enterocolitits, bronchopulmonary dysplasia, prolonged length of hospital stay, and death.

Paediatric hyponatraemia-related issues
Children (including neonates and older children) are at increased risk of developing hypoosmotic hyponatraemia as well as for developing hyponatraemic encephalopathy.
Plasma electrolyte concentrations should be closely monitored in the paediatric population.
Rapid correction of hypoosmotic hyponatraemia is potentially dangerous (risk of serious neurologic complications). Dosage, rate, and duration of administration should be determined by a physician experienced in paediatric intravenous fluid therapy.

Geriatric Use
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 impairment, and other diseases or concomitant drug therapy.

Blood
Glucose solution (an aqueous, i.e., electrolyte-free glucose solution) should not be administered through the same equipment as whole blood, as haemolysis and pseudoagglutination can occur.

4.5 Interaction with other medicinal products and other forms of interaction

Both the glycaemic effects of intravenous glucose and its effects on water and electrolyte balance should be taken into account when using intravenous glucose in patients treated with other substances that affect glycaemic control, or fluid and/or electrolyte balance.

Drugs leading to an increased vasopressin effect

The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and 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, e.g.: Chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics
- Drugs potentiating vasopressin action, e.g.: Chlorpropamide, NSAIDs, cyclophosphamide
- Vasopressin analogues, e.g.: Desmopressin, oxytocin, terlipressin

Other medicinal products increasing the risk of hyponatraemia also include diuretics in general and antiepileptics such as oxcarbazepine.

4.6 Fertility, pregnancy and lactation

Intrapartum maternal intravenous glucose infusion may result in foetal insulin production, with an associated risk of foetal hyperglycaemia and metabolic acidosis as well as rebound hypoglycaemia in the neonate.

Pregnancy
Glucose solution can be used during pregnancy. However, caution should be exercised when glucose solution is used intrapartum.

Glucose 50% w/v should be administrated with special caution for pregnant women during labour particularly if administered in combination with oxytocin due to the risk of hyponatraemia (see section 4.4, 4.5 and 4.8).

Fertility
There are no adequate data of the effect of Glucose on fertility.

Lactation
There are no adequate data of using Glucose solution during lactation. Glucose solutions have been used during lactation.

4.7 Effects on ability to drive and use machines

There is no information on the effects of intravenous glucose on the ability to operate a vehicle or other heavy machinery.

4.8 Undesirable effects

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

System Organ Class	*Adverse reaction (MedDRA term)*	*Frequency**
Immune system disorders	Anaphylactic reaction**	Not known
	Hypersensitivity**	Not known
Metabolism and nutrition disorders	Hyperglycaemia	Not known
	Hospital Acquired Hyponatraemia***	Not known
Skin and subcutaneous tissue disorders	Rash	Not known
Nervous system disorders	Hyponatraemic encephalopathy***	Not known
General disorders and administration site conditions	Chills	Not known
	Pyrexia	Not known
	Infection at site of injection	Not known
	Thrombophlebitis	Not known
	Infusion site reactions including, • Infusion site phlebitis • Infusion site erythema	Not known

* Cannot be estimated from the available data

** Potential manifestation in patients with allergy to corn, see section 4.4.

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

Other adverse reactions reported with glucose injection/infusions include:

- Infusion site thrombophlebitis (associated with hyperosmolar solutions)

- Adverse reactions reported when glucose is used with parenteral nutrition:

  Hepatic failure, Hepatic cirrhosis, Hepatic fibrosis, Cholestasis, Hepatic steatosis, Blood bilirubin increased, Hepatic enzyme increased, Cholecystitis, Cholelithiasis
  Pulmonary vascular precipitates

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 the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Prolonged administration or rapid infusion of large volumes of the product may cause hyperosmolarity and hyponatraemia, dehydration, hyperglycaemia, hyperglucosuria, osmotic diuresis (due to hyperglycaemia) and water intoxication and oedema. Severe hyperglycaemia and hyponatraemia may be fatal (see sections 4.4 and 4.8).
In case of suspected overdose, treatment must be stopped immediately. Management of overdose is symptomatic and supportive, with appropriate monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not applicable.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections
Concentrated Hydrochloric Acid

6.2 Incompatibilities

This solution should not be used in conjunction with additives incompatible with glucose, see section 6.6.

6.3 Shelf life

Unopened: 18 months

It is recommended that the product is used immediately after removal from the overpouch. From a microbiological point of view, any admixture 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. Preparation of the admixture should take place under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

For further information, see section 6.3.

6.5 Nature and contents of container

The product is a clear, colourless solution in a plastic Viaflex® container. The plastic is a PVC designated PL-146.

The containers are sealed in a plastic overpouch.

The solutions are supplied in 500ml, 1000ml, 1500ml, 2000ml and 3000ml fill volumes.

6.6 Special precautions for disposal and other handling

Dilution or addition to parenteral nutrition admixtures must take place in controlled and validated aseptic conditions.

The product should be inspected visually for particulate matter and discoloration after admixing and prior to administration. Do not administer unless the solution is clear and the seal is intact.

Check compatibility with other admixture components before use.

Additives known or determined to be incompatible with glucose as a diluent should not be used. The instructions for use of the medication to be added, including information on storage, must be consulted.

Before adding a substance or medication, verify that it is soluble and/or stable in water and that the pH range of the glucose solution is appropriate.

Mix the solution thoroughly when additives have been introduced.

Use of an in-line filter is recommended during administration of all parenteral solutions where possible.

Single use only.

Do not store partially used bags.

Discard any unused portion, waste materials and all associated devices.

<u>Risk of Air Embolism</u>

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 plastic 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.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

26/10/2019