SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Trade Name><Strength> concentrate for solution for infusion

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule (=20 ml) of concentrate for solution for infusion contains

Dipotassium phosphate 1.394 g

Potassium dihydrogen phosphate 0.544 g

*Electrolyte concentrations*

Potassium 1 mmol/ml

Phosphate 0.6 mmol/ml

Excipient(s) with known effect:

<Regarding the approval>

For a full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

<Regarding the approval>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

Phosphate substitution in intensive-care patients, with co-existing potassium deficiency, in whom close monitoring of serum potassium and phosphate concentrations can be performed.

* 1. Posology and method of administration

Posology

The dose is adjusted according to the actual basic or correction requirements, according to the analytical values of the serum electrolyte concentrations.

*Adults:*

In the setting of parenteral nutrition the basic phosphate requirement in adults is 0.3-0.5 mmol per kg body weight (BW) per day, corresponding to 0.5-0.8 ml per kg BW per day.

In therapy of severe hypophosphataemia the dose is adjusted according to the serum phosphate concentration. Then higher amounts than those stated above may be needed.

Per 0.6 mmol phosphate 1 mmol of potassium is administered.

The maximum daily dose of potassium is 2-3 mmol per kg BW.

*Paediatric patients:*

The dose should be adjusted strictly according to the prevailing serum potassium and phosphate concentrations which may be affected by fluid retention, dehydration or excessive water losses.

In children potassium intake during parenteral nutrition is recommended not to exceed 1-3 mmol/kg body weight per day.

Parenteral phosphate requirements in children above 1 year are adequately met with 0.2 mmol/kg body weight per day. Children below 1 year of age require in total up to 0.5 mmol/ kg body weight per day.

*Elderly patients:*

As for adults.

*Other special patient groups:*

See section 4.4.

Maximum infusion rate

The infusion rate is limited by the potassium content of the solution. The maximum infusion rate is 20 mmol of potassium per hour, corresponding to 0.3 mmol of potassium per kg BW per hour.

Method of administration

Intravenous use.

Only to be administered diluted as an additive to infusion solutions. The concentration of potassium in the infusion solution must not exceed 40 mmol/l (corresponding to 24 mmol/l of phosphate). For further details regarding dilution and suitable diluents see section 6.6.

Infusion should be carried out continuously. Use of infusion pumps is advisable.

Particular care should be taken to ensure that infusion is strictly intravenous, because paravenous administration can lead to tissue necrosis and to indurations and chalky deposits in the subcutaneous tissue.

* 1. Contraindications

Potassium Phosphate 1mmol/ml + 0.6mmol/ml must not be administered in cases of:

* Hyperphosphataemia
* Hyperkalaemia
* Hypocalcaemia
* Renal insufficiency
* Disorders that are frequently associated with hyperkalaemia such as dehydration, diabetic ketoacidosis, limited renal excretion, Addison’s disease, Familial periodic paralysis (*Adynamia episodica hereditaria*, Gamstorp’s syndrome), tumour lysis syndrome (TLS), sickle cell anaemia,
* Therapy with potassium sparing diuretics.
  1. Special warnings and precautions for use

Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml should only be administered with particular caution in cases of cardiac decompensation.

Administration should be discontinued if there are signs of renal insufficiency.

Sudden discontinuation of potassium administration may be followed by marked hypokalaemia, which may lead to increased toxicity of cardiac glycosides taken concomitantly.

Disturbances of the potassium balance, i.e. hyper or hypokalaemia, lead to typical alterations in the ECG. There is, however, no linear relationship between the ECG alterations and the potassium concentration in serum.

Since high levels of phosphate administration can cause hypocalcaemia and metastatic calcifications, the ionized calcium and phosphate should be monitored regularly if daily phosphate substitution exceeds 50 mmol.

Clinical monitoring should include regular checks of the serum electrolyte concentrations.

During phosphate substitution the plasma phosphate concentration and the amount of phosphate excreted in 24 hour urine should be monitored once weekly.

When high doses of phosphate are administered it can be necessary to administer calcium simultaneously. The calcium must be administered by a separate route.

Since per 0.6 mmol phosphate the solution contains 1 mmol of potassium, the potassium concentration should be taken into account when calculating the electrolyte balance.

When carrying out phosphate substitution as a part of parenteral nutrition, account should be taken of the fact that various solutions used for parenteral nutrition (including lipid emulsions) already contain phosphate.

* 1. Interaction with other medicinal products and other forms of interaction

*Cardiac glycosides:*

An increase of the intracellular potassium concentration weakens the effect of cardiac glycosides, a decrease of the intracellular potassium concentration increases the arrhythmogenic effect of cardiac glycosides.

*Suxamethonium:*

Marked hyperkalaemia may also result from simultaneous administration of potassium and suxamethonium.

*Other phosphate-containing medicinal products:*

Other phosphate-containing medications used with potassium phosphates may cause high blood levels of phosphate and may increase the risk of hyperphosphataemia, especially in patients with renal disease. Potassium sparing diuretics, aldosterone antagonists, Angiotensin Converting Enzyme (ACE) inhibitors, tacrolimus, ciclosporin, non- steroid anti-inflammatory drugs, peripheral analgesics and long-term heparin use These reduce the renal potassium excretion. Potassium administration simultaneously with those drugs may result in severe hyperkalaemia.

*Salicylates:*

Concurrent use of salicylates with potassium phosphates may increase plasma concentrations of salicylates since salicylate excretion is decreased in acidified urine.

*Interaction with food or beverages:*

None.

* 1. Fertility, pregnancy and lactation

Pregnancy

For Potassium Phosphate 1 mmol/ml +0.6 mmol/ml no data from clinical studies on exposed pregnancies are available. Animal studies with respect to pregnancy, embryonal/foetal development, parturition or postnatal development are not available either. However, no findings are known indicating direct or indirect harmful effects in that respect.

Caution should be exercised when prescribing the product to pregnant women.

Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml should only be administered during pregnancy if its benefits outweigh its possible risks.

Fertility

No data available.

Breast-feeding

It is not known if phosphates are secreted into breast milk. However, no problems in the breast-feeding of infants have been documented with intake of normal daily recommended amounts.

Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml should only be administered during breastfeeding if its benefits outweigh its possible risks.

* 1. Effects on ability to drive and use machines

Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml has no influence on the ability to drive and use machines.

* 1. Undesirable effects

Normally adverse effects are dose-dependent and are likely to occur only if an overdose of Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml is administered or if the administration rate is too high (symptoms see section 4.9). Nevertheless, if the product is administered in accordance to the instructions given, the following adverse effect has been detected.

Definition of frequency terms used in this section

Rare (≥1/10,000 to <1/1,000)

|  |
| --- |
| Gastrointestinal disorders   * Rare:  Nausea |

Information on particular undesirable effects

Drug interactions (see above) or suddenly occurring acidosis, acute impairment of renal function and other conditions may lead to sudden hyperkalaemia. Symptoms of hyperkalaemia see section 4.9.

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 Health Product Vigilance Center; HPVC, Thai FDA.

* 1. Overdose

Overdose can lead to hyperkalaemia and hyperphosphataemia.

*Symptoms associated with hyperkalaemia:*

The neuromuscular symptoms encompass fatigue, states of confusion, unexplained anxiety, weakness or heaviness of limbs, muscle twitching, paraesthesia, breathing problems, ascending paralysis.

Cardiac arrhythmia may occur due to hyperkalaemia or too rapid infusion.

Plasma potassium concentrations of 6.5 mmol/l or more are dangerous, concentrations above 8 mmol/l often lethal.

*Symptoms associated with hyperphosphataemia:*

Hyperphosphataemia may lead to

* renal damage as a result of the precipitation of calcium phosphate (nephrocalcinosis)
* the precipitation of calcium phosphate in other tissues (e.g. skin, cornea, lungs)
* and to hypocalcaemia (symptoms: convulsions, muscle cramps, tremor, numbness, tingling, pain or weakness in hands or feet; shortness of breath, or troubled breathing), up to hypocalcaemic tetany and metastatic calcification (see also section 4.4).

Treatment

Immediate discontinuation of infusion, slow intravenous administration of 10% w/v calcium gluconate, glucose infusions together with insulin, increase of diuresis or ion exchangers administered orally or rectally, correction of acidosis if necessary. In cases of massive overdose haemodialysis may be necessary.

1. PHARMACOLOGICAL PROPERTIES
   1. Pharmacodynamic properties

*Pharmacotherapeutic group:*

IV solution additives, potassium phosphate, incl. combinations with other potassium salts

ATC code: B05XA06

Pharmacodynamic properties of phosphate

Mechanism of action, therapeutic effect the total quantity of inorganic phosphate in an adult is approx. 0.7 kg. The major proportion of this is present in the form of inorganic phosphate compounds in the bones and teeth. Ionised inorganic phosphate is present in the plasma in the form of NaH2PO4. Ionised phosphate acts as a buffer in the intracellular space, in the blood and in the urine.

Phosphate deficiency syndrome can occur if insufficient phosphate is administered during parenteral nutrition. Particularly when large quantities of carbohydrate are administered there is a large uptake of phosphate by the cells thus leading to a diminution of the blood phosphate concentration.

*Other pharmacological effects:*

The pharmacodynamic effects of phosphate in Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml are essentially the same as in normal physiology. Thus, when administered as specified, no further pharmacodynamic effects have to be expected.

Pharmacodynamic properties of potassium

*Mechanism of action, therapeutic effect:*

As principal intracellular cation, potassium has two major physiological functions: maintenance of intracellular tonicity and transmembrane potential.

It is essential for transmission of nerve impulses, and contraction of cardiac, skeletal and smooth muscle. Potassium further participates in carbohydrate utilisation and protein synthesis.

The daily requirements for potassium are about 1 - 1.5 mmol per kg body weight.

Hypokalaemia is accompanied by muscle weakness, atony of gastro- intestinal smooth muscles (constipation up to paralytic ileus), loss of capability of kidneys to concentrate urine, ECG alterations and cardiac arrhythmia.

*Other pharmacological effects:*

The pharmacodynamic effects of potassium in Potassium Phosphate 1 mmol/ml + 0.6 mmol/ml are essentially the same as in normal physiology. Thus, when administered as specified, no further pharmacodynamic effects have to be expected.

* 1. Pharmacokinetic properties

Phosphate

*Absorption*

As the solution is intended for intravenous use its bio-availability is 100%.

*Distribution*

Phosphate is the relevant form of phosphorus in the human body. Approx. 85 per cent of the total body phosphorus is stored in bone. Of the remainder, 14 per cent occurs in soft tissues and 1 per cent is found in the blood.

*Biotransformation*

Phosphate underlies no metabolism in the strict sense.

*Elimination*

Phosphate is predominantly excreted via the kidneys. Parathormone, calcium administration, oestrogen, thyroxine and acidosis increase the renal excretion of phosphate; cholecalciferol, growth hormone, insulin and cortisol have the effect of reducing it. The phosphate and calcium balances are closely linked to each other.

Potassium

*Absorption*

As the solution is intended for intravenous use its bio-availability is 100%.

*Distribution*

Potassium is the most important cation of the intracellular space, approx. 98 per cent of the organism’s total potassium being located there. The intracellular potassium concentration is approx. 140 - 150 mmol/l. The normal potassium concentration in plasma is between 3.5 and 5 mmol/l

*Biotransformation*

Potassium underlies no metabolism in the strict sense.

Potassium is mainly excreted in urine (about 90 per cent) and about 10 per cent are excreted via the gastro-intestinal tract.

Even in situations of potassium deficiency 10 - 50 mmol of potassium are renally excreted per day. Potassium deficiency may be caused by increased renal excretion, increased gastro-intestinal losses, e.g. by vomiting or diarrhoea, or through fistulae, by increased intracellular uptake, e.g. during therapy of acidosis or therapy with glucose and insulin, or by insufficient potassium intake.

* 1. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<Regarding the approval>

* 1. Incompatibilities

<Regarding the approval>

* 1. Shelf life

<Regarding the approval>

* 1. Special precautions for storage

<Regarding the approval>

* 1. Nature and contents of container

<Regarding the approval>

* 1. Special precautions for disposal

<Regarding the approval>

1. MARKETING AUTHORISATION HOLDER

<Regarding the approval>

1. MARKETING AUTHORISATION NUMBER(S)

<Regarding the approval>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Regarding the approval>

1. DATE OF REVISION OF THE TEXT1

<Regarding the approval>