**sp.zn. sukls187999/2018**

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Potassium dihydrogen phosphate Ardeapharma 68 mg/ml concentrate for infusion solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1000 ml of concentrate for infusion solution contains kalii dihydrogenophosphas 68.0 g.

| | |
|---|---|
| $K^+$ | 500 mmol/l |
| $H_2PO_4^-$ | 500 mmol/l |

500 mmol of $H_2PO_4^-$ represents the equivalent of 15.5 g of phosphorus.

For the full list of excipients, see the section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for infusion solution

Description of the product: clear, colourless solution

| | |
|---|---|
| Osmolality | 810 mosmol/kg |
| pH | 3.5 - 5.5 |

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

The therapy of severe or less severe depletion of phosphates with hypophosphatemia from various reasons associated with potassium depletion with hypokalaemia provided that the condition is not possible to be managed by oral supplementation.

The supply of phosphate and potassium ions during total or supplemental parenteral nutrition.

The product is suitable for adults.

The use in children is limited only to the therapy of severe depletion of phosphates with hypophosphatemia accompanied by potassium depletion with hypokalaemia.

### 4.2 Posology and method of administration

Posology

The dosage is individual, guided by the need of potassium and phosphate administration. Plasma levels of these electrolytes indicate the need of potassium and phosphate administration together with the patient's clinical condition and therapeutic method taken into account.

In patients with impaired renal function or cardiac disorders, plasma levels and ECG should be monitored and the dosage adjusted if need be.

The infusion solution is most often administered so that the total daily dose of phosphates is 0.2 – 0.5 mmol/kg up to maximum daily dose of 50 mmol. Potassium dihydrogen phosphate is administered in a carrying solution (see below). Final potassium and phosphates concentrations after dilution in a carrying solution should not exceed 40 mmol/l.

The following table can be used for the correct dosage of potassium dihydrogen phosphate in adults:

| | **The rate of administration*** | | |
|---|---|---|---|
| **Serum phosphate levels** | **Body weight 40 – 60 kg** | **Body weight 61 – 80 kg** | **Body weight 81 – 120 kg** |
| < 0.3 mmol/l | 25 - 30 mmol/day | 35 - 40 mmol/day | 40 - 60 mmol/day |
| 0.3 – 0.6 mmol/l | 10 - 25 mmol/day | 15 - 30 mmol/day | 20 - 40 mmol/day |

| | | | |
|---|---|---|---|
| (in cases when oral correction is impossible) | | | |

**The rate of administration should be adjusted according to the clinical condition and renal functions.*

Special patient groups (see also the section 4.4)

Liver function disorder

During the therapy and nutritional support in patients suffering from hepatic insufficiency, concurrent deficiency of both potassium and phosphate is threatening. In such cases, potassium dihydrogen phosphate is suitable to supplement both of the electrolytes deficiency and to prevent so called refeeding syndrome (see the section 4.4).

A daily dose of potassium dihydrogen phosphate in liver diseases and hepatic insufficiency is dependent on the size of deficiency. Common daily dose of phosphates is 16 - 40 mmol. In case of depletion, the dose of phosphates is increasing according to the need and serum levels; maximum daily dose of 100 mmol is the most frequent one but it can be even higher.

Renal function impairment

In patients with renal function impairment, it is advisable to adjust (usually to decrease) the daily administered dose of the solution of potassium dihydrogen phosphate.

Malnutrition

In patients with malnutrition receiving the glucose solution (often together with the solution of amino acids and a fat emulsion), the administered dose of potassium dihydrogen phosphate as the dose between 20 and 25 mEq per each 1 000 kcal of a nutritional support can be recommended.

Paediatric population

In children, potassium dihydrogen phosphate is indicated only in cases of severe depletion of phosphates with hypokalaemia.

| Age group | Phosphates (mmol/kg$^{-1}$) | Potassium (mmol·kg$^{-1}$) |
|---|---|---|
| The immature | 0.8 - 2 | 2 - 5 |
| 0 - 6 months | 0.7 – 1.3 | 1 - 3 |
| 7 - 12 months | 0.5 | 1 - 3 |
| 1 - 18 years | 0.2 – 0.7 | 1 - 3 |

Parenteral nutrition in children

In children, potassium dihydrogen phosphate is not indicated as a part of parenteral nutrition. It should not to be administered as a part of parenteral nutrition for the reason that a precipitation with bivalent cations ($Ca^{2+}$, $Mg^{2+}$) may occur.

During parenteral nutrition in new-borns, a calcium solution always should be administered. This solution is precipitated with inorganic phosphate and thus also with the solution of potassium dihydrogen phosphate while insoluble clot is developed.

In new-borns and small children requiring a parenteral nutrition, organic phosphate salt has to be used, and thus the solution of potassium dihydrogen phosphate is contraindicated (see the section 4.3).

Method of administration

The preparation is administered in a carrying solution, particularly in glucose solutions with the concentrations from 5% to 40% or saline solution. Potassium concentration in final administered infusion solution may not exceed 40 mmol/l; the maximum rate of potassium supply into the organism is 20 mmol/hour for adult patients. The infusion with potassium dihydrogen phosphate is usually administered continually for the period of 12 - 24 hours, the rate can be different in cases of severe and life threatening coincident depletion of both potassium and phosphate in the organism.

## 4.3 Contraindications

Hyperphosphatemia and/or hyperkalaemia and/or hypocalcaemia

The administration of the potassium dihydrogen phosphate solution is contraindicated in cases where high doses of calcium or magnesium should be administered (especially in new-borns and small children). For that reason the potassium dihydrogen phosphate solution is contraindicated in the immature, new-borns, sucklings and small children that require the complete parenteral nutrition. See also the section 4.2.

## 4.4 Special warnings and precautions for use

The preparation must not be used in patients with potassium plasma levels higher than 4.5 mmol/l and phosphates plasma levels higher than 2.4 mmol/l.

Potassium dihydrogen phosphate should be cautiously administered in patients suffering from heart failure, peripheral or pulmonary oedema, renal function impairment or conditions with the tendency to hyperkalaemia.

Potassium, phosphate as well as calcium serum levels and other basic homeostasis parameters should be monitored during the period of potassium dihydrogen phosphate administration. An appropriate rate of infusion administration should be maintained.

Continuous monitoring of acid base balance, serum electrolytes, ECG and clinical patient's condition are recommended to be performed during the therapy of electrolytes depletion in acidosis. Potassium salts should be used cautiously in conditions associated with heart blocks because an increased kalaemia can make the degree of heart block higher.

Potassium dihydrogen phosphate is not possible to be used as the only source of potassium in all patients. It regards particularly growing children, adolescents or rehabilitating patients where the need of potassium is expected to be higher than the need of phosphates. That is the reason why in this group of patients, the required potassium dose should be administered also in a form of potassium chloride.

Phosphates must cautiously be administered in patients with predisposition to hyperphosphatemia such as patients with hypoparathyreosis, chronical renal disease, rhabdomyolysis, acute dehydration, acute pancreatitis, serious renal function impairment and extensive tissue damage (serious burns).

Phosphates must cautiously be administered in patients with low calcium serum levels because these levels can be further lowered during a high rate of the phosphates administration. Hypocalcaemia can be expected in conditions such as hypoparathyreosis, osteomalacia, chronic renal diseases, acute pancreatitis, rhabdomyolysis, rachitis, myotonia congenita or heart disease (especially in digitalized patients, see Interactions).

In patients with impaired potassium excretion (particularly patients with chronic renal disease), the potassium salts administration can induce hyperkalaemia. Resulting heart function impairment may not be visible on the ECG curve. A continuous monitoring of electrolytes blood levels is recommended, in which case not only absolute potassium concentration but also the speed of an increase in potassium blood levels are determinative.

<u>Renal function impairment</u>

In patients with chronic kidney disease in the grades 3 or 4, serum levels of potassium, calcium, phosphate and alkaline phosphatase should be monitored during each check of serum creatinine or eGFR.

Phosphate is actively eliminated via kidneys and the retention of phosphate is increased together with the impairment of renal function. That is the reason why phosphate should cautiously be used in patients with serious renal function impairment. A worsened elimination followed by an increase in plasma levels cause a higher risk of insoluble phosphates formation.

It is useful to add potassium dihydrogen phosphate into the dialysate solution up to the final concentration of 1 mmol/l to prevent hypophosphatemia during the dialysis therapy. This can be performed also in children.

In case of a decreased renal function with a parallel use of renin-angiotensin system antagonists, potassium levels should be monitored before the start of the therapy and then in regular intervals or in case of any change of the dose. In case of the use of alfa-calcidiol or calcitriol, also phosphate blood level should be monitored.

<u>Respiratory failure</u>

A low phosphates level is critical for the function of respiratory muscles. In case of a severe depletion associated with respiratory failure, a phosphate supply is increased (by an increase in a rate of infusion administration, an increase in potassium dihydrogen phosphate in the infusion or by a repeated infusion).

Cardiac failure
Potassium and phosphate blood levels should be checked and also renal function should be assessed before the administration of potassium dihydrogen phosphate solution. This procedure should be performed and repeated, especially in case of parallel administration of drugs from the group of ACE inhibitors, mineralocorticoid or angiotensin II receptors antagonists. During the administration, ECG should be monitored.

Diabetic ketoacidosis
In patients suffering from diabetic ketoacidosis, phosphate should be administered only in case of insulin effect onset which is usually connected with severe hypophosphatemia that can within 48 hours result in muscular weakness associated with respiratory failure and hypoxia. If phosphate level during the therapy is normal or increased, then phosphate is not an essential part of the therapy of diabetic ketoacidosis.

The administration of potassium dihydrogen phosphate in patients with diabetic ketoacidosis is not recommended during the initial haemodynamic resuscitation if potassium serum level persists above 5.5 mmol/l. In cases when potassium serum level is lower than 5.5 mmol/l and the patient's diuresis retained, the administration of 0.9% sodium chloride solution with 40 mmol/l of potassium is recommended. If potassium serum level drops below 3.5 mmol/l, potassium rate of administration should be increased.

In children with diabetic ketoacidosis, potassium dihydrogen phosphate may not be used as the only source of potassium.

Refeeding syndrome, parenteral nutrition
Refeeding syndrome is related to a significant decrease in phosphate and potassium concentrations in seriously undernourished patients receiving a nutritional support. The risk of refeeding syndrome onset is increased in patients with BMI lower than 16 $kg/m^2$, patients that lost more than 15 % of their body weight during the last 3 - 6 month, patients with a low nutritional intake for a period longer than 10 days, with low potassium, phosphates or magnesium levels before the nutrition administration, in patients with an alcohol abuse history and the patients treated with insulin, chemotherapeutics, antacids or diuretics.

In case of refeeding syndrome risk, phosphate levels should be monitored on the daily basis till the ions levels are stabilized, and then three times per week. An oral, enteral or infusion administration of potassium (2 to 4 mmol/kg/day), phosphates (0.3 – 0.6 mmol/kg/day), magnesium (0.2 mmol/kg/day intravenously or 0.4 mmol/kg/day orally) should also be considered in patients at risk of the development of refeeding syndrome. The exceptions are the cases when these electrolytes plasma levels before the nutrition administration are increased. The correction of plasma levels before the nutrition administration is not necessary.

In chronically undernourished individuals, a long term administration of parenteral nutrition with a low content of phosphates can result in serious phosphate depletion and bone changes.

The solution may not be administered together with the solutions containing calcium (see also the section 6.2 Incompatibilities).

## 4.5 Interaction with other medicinal products and other forms of interaction

The preparation should be administered very cautiously in cases of parallel therapy with the drugs that cause a potassium level increase. A simultaneous increased calcium supply results in a higher risk of precipitation with potassium dihydrogen phosphate, which can cause embolism of the formed crystals into tiny vessels. The product of molar concentrations of inorganic phosphate and calcium in the solution should be lower than 80 mmol/l.

The preparation is necessary to be administered very cautiously in cases of parallel therapy with:

- catecholamines: risk of hypophosphatemia
- beta adrenergic agonists: risk of hypophosphatemia
- sodium hydrogen carbonate and acetazolamide: risk of hypophosphatemia
- in case of the use of alfacalcidol or calcitriol – serum phosphate should be monitored
- insulin: the insulin therapy results in a decrease in potassium an phosphate levels
- ACE inhibitors

- preparations containing calcium
- preparations containing other phosphates
- preparations containing potassium
- potassium sparing diuretics
- non-steroid anti-inflammation preparations (NSAIDs) and other analgesics
- cyclosporine, heparin
- digoxin
- suxamethonium
- corticosteroids and drugs influencing on the bone tissue metabolism, particularly mineralocorticoids: a higher risk of oedema formation
- salicylates: simultaneous potassium dihydrogen phosphate administration can cause an increase in salicylates concentration because the excretion of them is decreasing with urine acidification. When a salicylates level in the patient has been stabilized, the administration of potassium dihydrogen phosphate may cause an increase in salicylates levels up to the toxic levels.
- bisphosphonates: a parallel administration can induce hypocalcaemia

The preparation can cause an increase in urine acidity, and thus to have an influence on the elimination of some drugs.

Suxamethonium can cause a depolarisation of motor disks in skeletal muscles which results in an immediate increase in potassium plasma level. The increase is usually slight, about 0.5 mmol/l. Suxamethonium should not be used in patients with an increased potassium blood concentration such as the patients with renal function impairment or in patients to whom the potassium infusion is being administered.

### 4.6 Fertility, pregnancy and lactation

Pregnancy

Potassium dihydrogen phosphate has been used in the therapy for many decades. No adverse effects on the course of pregnancy or foetus/new-born health condition have been proved during the given period. During the administration of the preparation in pregnancy, however, it is advisable to proceed with caution taking into account an indirect impact on the embryo/foetus condition.

Lactation

The product can be used in breast-feeding women.

Fertility

Adequate toxicological studies in animals have not been performed. No negative effects on fertility are expected.

### 4.7 Effects on ability to drive and use machines

Not relevant.

### 4.8 Undesirable effects

Safety profile summary

No direct undesirable effects are present with the use of the product of Potassium dihydrogen phosphate Ardeapharma in case of its correct dosage and the observance of the rate of application. Rarely, a local irritation, pain in the administration site and/or local effects on the vessel wall – thrombophlebitis can be observed. High doses, high concentrations, a fast and/or long-term infusion can result in hyperkalaemia, hyperphosphatemia, hypocalcaemia, kidney disorders and/or heart activity, calcification of soft tissues and other complications connected with such conditions.

Undesirable effects list in table format

| Organ system class | Undesirable effect | Frequency of occurrence |
|---|---|---|
| Metabolism and nutrition disorders | Hyperkalaemia | Not known (cannot be determined from available data) |
| | Hyperphosphatemia | |
| | Hypocalcaemia | |

| | | |
|---|---|---|
| Nervous system disorders | Paresthesia | Not known.<br>(cannot be determined from available data) |
| | Hypocalcemic cramps | |
| Cardiac disorders | Arrhythmia | Not known.<br>(cannot be determined from available data) |
| Vascular disorders | Thrombophlebitis | Not known.<br>(cannot be determined from available data) |
| Renal and urinary disorders | Kidney damage | Not known.<br>(cannot be determined from available data) |
| General disorders and administration site conditions | Soft tissue calcification | Not known.<br>(cannot be determined from available data) |

Description of selected undesirable effects

Common symptoms of hyperkalaemia include paresthesia, muscular weakness, changes in cardiac rhythm, changes in ECG, confusion, apathy and/or hypotension.

Common symptoms of hypocalcaemia include nervous irritation, cramps or even tetany.

Reporting on suspicion of undesirable effects

Reporting on suspicion of undesirable effects after the medicinal product authorisation is important. It enables to continue with surveillance of benefits/risks ratio regarding the medicinal product. We ask the medical staff for reporting on suspicion of undesirable effects to the address:

Státní ústav pro kontrolu léčiv (State Institute for Drug Control)
Šrobárova 48
100 41 Praha 10
Website: www.sukl.cz/nahlasit-nezadouci-ucinek

### 4.9 Overdose

In case of overdose, hyperkalaemia manifesting with disorders of neuromuscular conduction (muscular weakness, paresthesia of limbs, paralyses, arrhythmia with the possibility of cardiac arrest) can occur. In case of symptoms of hyperkalaemia or the proof of hyperkalaemia, the potassium supply must be stopped immediately. The potassium excess can be eliminated from the organism after a sufficient hydration by the administration of diuretics with kaliuretic effect; in serious cases - haemodialysis is necessary.

The overdose can result in hyperphosphatemia and hypocalcaemia. In such cases, the infusion must be stopped immediately and a correction of calcium level should start.

Continual ECG monitoring is necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: blood substitutes, infusion and perfusion solutions; electrolyte solutions; potassium phosphate including combinations with other potassium salts

ATC code: B05XA06

Potassium dihydrogen phosphate is dissociated in aqueous environment including plasma. Potassium is the most frequent cation in intracellular space, phosphate is the dominant intracellular anion. The concentrated solution, intended for the preparation of infusion solutions, contains ions natural for the organism, is used for the correction of phosphor and/or potassium deficiency according individual needs of the patient.

### 5.2 Pharmacokinetic properties

General information – no active metabolites are generated with inorganic salts.

Characterization of the active substance – it is simple inorganic salt – body natural ions. It is water-soluble, fat-insoluble.

Characterization of the administration in patients – it is a product intended for intravenous use. Potassium is quickly distributed in the organism after i. v. administration. The concentration gradient between intracellular and extracellular compartments is maintained by the activity of the natrium-potassium pump. About 98 % of potassium in human body is present in intracellular compartment (prevailingly in skeletal muscles), into which is actively transported. About 95 % of potassium excreted is filtered by kidneys, the function of which is for potassium balance determinative.

Alkalosis is often connected with hypokalaemia while acidosis with hyperkalaemia. Potassium plasma levels thus in such conditions indicate abnormalities.

About 85 % of phosphates are contained intracellularly in bones and teeth. Phosphate levels are determined mainly by the distribution between the bones and extracellular compartment, by active resorption from the intestine and active filtration in the kidneys. Alkalosis and diabetic ketoacidosis are often associated with hypophosphatemia.

Potassium and phosphate are used by the cells in synthesis of macromolecules (anabolic processes). That is why the body demands on potassium and phosphate intake are increasing with an increased nutrients supply and after the renewal of food intake in undernourished patients. Children have increased demands on phosphate supply, and then plasmatic levels in children are commonly higher than in adult population.

### 5.3 Preclinical safety data

It is a product with a long-term usage („well implemented therapeutic use “) in which no preclinical studies had been performed with its introduction into the therapy. The preparation contains ions that are natural for the body. Preclinical data on the safety are related to other ways of administration.

Potassium dihydrogen phosphate showed neither toxicity nor teratogenic effects in pregnant mothers in doses up to 320 mg/kg/day p.o., resp. 282 mg/kg/day p.o. in mice, resp. rats. No teratogenicity has been shown in tests on chicken embryo either. In Ames test with *Saccharomyces cerevisiae* strain D4 and *Salmonella typhimurium* strains TA1535, TA1537 and TA1538, no mutagenic effect has been shown in tests either with or without metabolic activation. Acute toxicity of potassium dihydrogen phosphate is low, $LD_{50}$ = 3200 mg/kg p.o. in mice and 2820 mg/kg p.o. in rats.

## 6. PHARMACEUTIAL PARTICULARS

### 6.1 List of excipients

Aqua pro iniectione

### 6.2 Incompatibilities

The preparation may not be mixed with solutions containing calcium or magnesium; a precipitation of particles in the solution (insoluble phosphates) can be developed. The precipitation can also be developed after the mix with solutions containing iron or aluminium salts. The infusion should not be applied simultaneously with the administration of these substances in any way of application.

The preparation may not be added to/diluted by Hartmann or Ringer infusion solutions including the Ringer infusion solution with sodium-lactate.

The preparation should not be mixed with the preparations containing ciprofloxacin, dobutamine hydrochloride, dolasetron, pantoprazolum natricum, amiodarone hydrochloride, caspofungin acetate, ceftaroline fosamil or doripenem.

### 6.3 Shelf life

3 years provided that the package is intact.

Shelf life after the first opening/dilution:

Chemical and physical stability before the use after the opening was confirmed for 48 hours at 25°C.

Chemical and physical stability after the dilution with an isotonic NaCl solution or with 5% up to 40% glucose solutions was confirmed for 24 hours at 25 °C.

From microbiological point of view, the product should be used immediately. If it is not used immediately, then the period and storage conditions of the product after the opening before the use are within the reliability of the user and in common case it should not be longer than 24 hours
at 2-8 °C as far as the opening/dilution was not performed under the controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Protect from frost.

### 6.5 Nature and contents of container

Infusion glass bottle with a rubber stopper and a metallic closure, carton box.

Package size: 1x 80 ml, 1x 200 ml, 20x 80 ml, 10x 200 ml

Not all package sizes may be marketed.

### 6.6 Special precautions for use, disposal and other handling

**The product must not be used undiluted!**

It can be diluted with an isotonic sodium chloride solution or with 5% up to 40 % glucose solutions.

Parenteral products should be checked up visually before the use. The product must not be administered if visible solid particles are present or the package is not intact.

The infusion product is a concentrated solution, and thus should not be stored at the temperatures lower than the common room temperature. Crystals, which may be developed during the storage, can be dissolved by warming the bottle. It is necessary to use the infusion set provided with the filter as a precautionary measure against unintentionally infused crystals in the solution.

The preparation is intended only for a single use.

Any unused product or waste should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

ARDEAPHARMA, a.s., Třeboňská 229, 373 63 Ševětín, Česká republika

## 8. MARKETING AUTHORISATION NUMBER(S)

39/138/18-C

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 5th March 2020

Date of the last renewal of the authorization:

## 10. DATE OF REVISION OF THE TEXT

5th March 2020