# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

PRE-EKLAMOL MAGNESIUM SULPHATE 40 g/1000 ml Solution for I.V. Infusion
Admistered intravenously.
Sterile

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active ingredient*:***
Each 1000 ml solution contains 40 g magnesium sulphate heptahydrate.
(Each 4mmol $Mg^{++}$ =1g magnesium sulphate = 8 mEq $Mg^{+2}$)

pH: 4,5-7

**Excipients:**
For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Sterile solution for intravenous infusion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PRE-EKLAMOL MAGNESIUM SULPHATE 40 g/1000 ml is indicated for the prevention of eclampsia and control of seizures in severe pre-eclampsia. This product has been produced for maintenance therapy following a 4 g IV loading dose.

### 4.2 Posology and method of administration

**Posology / frequency and duration of application:**
**Eclampsia:**
PRE-EKLAMOL MAGNESIUM SULPHATE 40 g/1000 ml is for intravenous use only.
For the treatment of pre-eclampsia or eclampsia, intravenous infusion of magnesium dilute solutions (4%) is administered. Therefore, in the following clinical conditions, both types of treatment are considered appropriate.

**MAGNESIUM SULPHATE REGIME AND TRACKING:**
The most preferred regimen for magnesium sulphate; The dose of 4-6 g IV is administered in 15-20 minutes, followed by 2 g of continuous infusion per hour. The therapeutic dose of magnesium sulphate is 3.95 to 6.90 mEq/L, and serum magnesium levels should be monitored every six hours. The maintenance phase is administered only if patellar reflex is present (loss of reflex is the first sign of symptomatic hypermagnetemia), if the respiration is more than 12 per minute and the urinary outlet is above 100 ml every four hours. Although magnesium sulphate is usually continued for postpartum 24 hours, there have no a high-quality data that determines the time of discontinuation of the drug. In women with mild pre-eclampsia, 12

hours may be sufficient, while anticonvulsant therapy should be continued for 24-48 hours in women with severe pre-eclamptic and eclampsia.
If magnesium sulphate is administered to pregnant women continuously for 5-7 days, hypocalcemia and bone anomalies may occur in the developing fetus. These bone anomalies include demineralization and osteopenia in the skeleton. In addition, newborn fractures have also been reported. The short-term treatment that poses a fetal risk is not known. Magnesium sulphate should only be used during pregnancy when it is very necessary. If magnesium sulphate is given for the treatment of preterm labor, the expectant mother should be informed that the efficacy and safety of this use is not known precisely and that the use of 5-7 days may cause fetal anomalies.

**For the prevention of convulsions in pregnancy toxemia;** After administering 4 g/ 100 ml IV solution for infusion in 15-20 minutes, 12 to 15 drops per minute are given in the form of 40 g / 1000 ml IV solution for infusion.

**Method of Application:**
PRE-EKLAMOL MAGNESIUM SULPHATE 40 g/1000 ml is used only intravenously.

**Additional information on special populations:**
**Impaired renal function:**
In patients with severe renal insufficiency, serum magnesium concentrations should be checked frequently, and the maximum magnesium sulphate dose should not exceed 20 g per 48 hours.
**Impaired hepatic function**
All magnesium is excreted through the kidneys. No dose adjustment is required in liver failure.
**Elderly population**
No special dose adjustment is required, provided there is no renal impairment.

**4.3. Contraindications**
Magnesium sulphate is contraindicated in patients with heart block, myocardial damage, severe renal failure, or hypersensitivity to magnesium sulphate or magnesium sulphate salts. For mothers with pregnancy toxemia during the two hours before delivery I.V. Magnesium should not be applied.
Magnesium sulphate is contraindicated in patients with Myasthenia Gravis as it may precipitate severe myasthenic crisis. On the other hand, the use of magnesium sulphate with calcium channel blockers may lead to hypotension.

**4.4 Special warnings and precautions for use**
FETAL RISK:
In case of renal failure, parenteral use may lead to magnesium intoxication. Since magnesium is completely excreted from the body through the kidneys, the drug should be used with caution in patients with renal failure. Urine excretion should be continued 100 ml every four hours. The monitoring of serum magnesium level and the clinical condition of the patient is necessary to avoid the overdose in toxemia.

| **Toxicity table:** | |
|---|---|
| Results | Magnesium level mg/dl (mEq/L) |
| Normal pregnancy level | 1,5-2,5 |
| Therapeutic level | 4-8 |
| Patellar reflex loss | 8-12 |
| Respiratory depression | 9-12 |
| Sleep-state cardiac arrest | 10-12 |

As an antagonist I.V. Calcium (5-10 mEq) can be used.

Magnesium sulphate solution should be applied slowly against the risk of hypermagnesemia.

**4.5 Interaction with other medicinal products and other forms of interaction**
PRE-EKLAMOL MAGNESIUM SULPHATE 40 g/1000 ml may be inconvenient to use with the following drugs:
• Digitalis glycosides used in heart disease (eg digoxin, digidin),
• Miyorelaxanes used in anesthesia (Use with magnesium sulphate may increase the effect of such drugs),
• High doses of opioid (eg morphine), barbiturate (eg amylobarbitone) or hypnotic drugs (eg nitrazepam) (use with magnesium sulphate may cause respiratory depression),
• Calcium channel blockers such as nifedipine or nimodipine (use with magnesium sulphate may cause problems in muscle functions),
• Aminoglycoside antibiotics (eg streptomycin) may increase the neuromuscular blocking effect of parenteral magnesium.
• Following administration of drug or drug groups such as Aminoglycosides, Cyclosporine, Digitalis, Alcohol, Amphotericin B, Diuretics, Cisplatin, renal loss of drug-induced magnesium is observed.
• Use with any other drug, including non-prescription medicines, may be inconvenient.
• Since the absorption of drugs containing levothyroxine PRE-EKLAMOL Magnesium Sulfate 40 g/1000 ml, the two drugs should be taken at least 2 hours apart.

**Additional information about special populations:**
No data is available.

**Pediatric population:**
No data is available.

**4.6 Pregnancy and lactation**
**General advice**
Pregnancy Category: D

**Women with childbearing potential / Contraception**
When administered with continuous IV infusion (especially 24 hours before delivery) to control convulsions in toxemic women, signs of magnesium toxicity, such as neuromuscular or respiratory depression, may be observed in the newborn.

**Pregnancy**
**Early birth;** Initial dose: IV 4-6 g Magnesium Sulphate (32-48 mEq magnesium) is administered by IV infusion in 20-30 minutes. Maintenance dose: 1-3 g magnesium sulphate per hour (8 - 24 mEq of magnesium) in IV infusion is given until the uterine contractions stop. Dosage limits for adults: Up to 40 g magnesium sulphate (320 mEq magnesium) per day can be administered.
Continuous administration of magnesium sulphate to prevent premature birth is an unapproved treatment. Efficacy and safety of such use has not been detected. The application of Magnesium Sulphate Solution for Infusion outside the approved indication in pregnant women should be performed by experienced personnel in the presence of the appropriate obstetric protective facility in the hospital environment.

**Lactation period**
It is not known whether Magnesium Sulphate is excreted in breast milk. Since many drugs pass into breast milk, Magnesium Sulfate Solution for Infusion should be cautious when applying to women who are breastfeeding.

**Fertility**
No data is available.

**4.7 Effects on ability to drive and use machines**
It is not valid, as it is impossible to apply Magnesium Sulfate Solution for Infusion during vehicle and machine use.

**4.8 Undesirable effects**
The undesirable effects of parenterally administered magnesium are usually the result of magnesium intoxication. These include burning in face, sweating, hypotension, suppression of reflexes, weak paralysis, hypothermia, circulatory collapse, cardiac and central nervous system depression prior to respiratory system paralysis.
Hypocalcemia associated with tetany symptoms due to magnesium sulphate treatment for eclampsia has been reported.

**4.9. Overdose and treatment**

**Symptoms:**
Magnesium intoxication occurs with sharp drop in blood pressure and respiratory system paralysis. The disappearance of the patellar reflex is one of the useful clinical signs used to

detect magnesium intoxication. In case of overdose, artificial ventilation should be performed until calcium salt IV is injected to antagonize the effects of magnesium.

**Treatment:**
Artificial ventilation is often necessary. 10 to 20 ml of the 5% of intravenous calcium solution (diluted with isotonic sodium chloride if necessary) is used to reverse the effects of hypermagnesemia. Subcutaneous physostigmine, 0.5 to 1 mg may be useful.
In newborns, resuscitation may be necessary in neonates and endotracheal intubation or intermittent positive pressure ventilation assisted ventilation or IV calcium administeration is performed.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
**Pharmacotherapeutic group:** Mineral solutions
**ATC code:** A12CC02
Magnesium ion (Mg + 2) is the second most common cation in intracellular fluid. It joins to the function of many enzymes as cofactor. It plays an important role in neurochemical pulse transmission and muscle excitability. The mechanism of action is not fully known. Magnesium can suppress neuromuscular liquefaction by inhibiting the release of acetylcholine in the mionural junction. It may also have depressant effect on smooth muscles and depress the central nervous system. Therapeutic serum concentrations as anticonvulsant are 4-7 mEq/L. Elimination depends on plasma concentration and glomerular filtration rate. Magnesium is the cofactor in enzymes that use adenosine triphosphate (ATP) and other nucleotide triphosphates as substrates. The binding of the mRNA to the ribosomes and the integration of the ribosomes requires $Mg^{+2}$ ion. Total body magnesium (for 70 kg) is up to 2000 mEq. 50% of this is found in bone, 45% in intracellular fluid and 5% in plasma. The concentration of $Mg^{+2}$ in the plasma is 1.6-2.6 mEq/L, of which 2/3 is ionised (free), 1/3 is bind to proteins. The concentrations of intracellular and extracellular $Mg^{+2}$ may vary independently. Magnesium inhibits neuromuscular communication at levels above the physiological level in plasma (> 2.06 mEq/L), shows anticonvulsant action and causes depression in the central nervous system. It has been suggested that the release of acetylcholine from the motor nerve endings decreases with the increase of magnesium above the physiological limits. When serum concentrations of magnesium exceed 4 mEq/L, deep tendon reflexes decrease and disappear above 10 mEq/L. These levels may cause respiratory paralysis and a complete heart block. Concentrations above 12 mEq/L may be fatal. In experimental studies, it has been reported that $Mg^{+2}$ ions slow the impulse formation in the sinoatrial node of the heart and prolong the conduction time. I.V. Magnesium infusions have been reported to prolong the PR interval, H interval (atrial-His bundle range), anterograde AV nodal effective refractory period and sinoatrial conduction time. Magnesium also has a peripheral vasodilator effect. It causes flushing and sweating at moderate doses, and hypotension at high doses. The depressant effect of magnesium on the neuromuscular plate and the central nervous system can be antagonized by giving calcium.

**5.2 Pharmacokinetic properties**

**General properties**

Absorption:

Intravenously administered magnesium sulphate is rapidly absorbed and lasts for about 30 minutes.

Distribution:

Approximately 1-2% of the total magnesium in the body is found in the extracellular fluid cavity. Magnesium is bound to albumin at rate of 30%.

Biotransformation:

Magnesium is not metabolized.

Elimination:

The major excretion path of magnesium is the kidneys. The amount excreeded is proportional to the magnesium concentration in the blood and the glomerular filtration rate.

Linearity / non-linearity:

No data is available.

**5.3 Preclinical safety data**

Acute oral toxicity of magnesium compounds is low. The oral LD50 values in the rat were 2800 mg/kg for magnesium chloride and 5440 mg/kg for nitrate. Toxicity symptoms are hypotension and respiratory paralysis by oral administraion, general anesthesia and narcosis by I.V. administration.

The carcinogenic effect of magnesium compounds has not been investigated. However, no such effect was reported in the clinic. Magnesium compounds are not found in carcinogen substance indexes. The mutagenic activity of magnesium chloride was investigated by the Salmonella assay and a weak mutagenic effect was reported.

Teratogenicity and reproductive toxicity of magnesium compounds have not been investigated. However, when administered to pregnant women due to eclampsia or as tocolytic, no teratogenic effect was observed.

Congenital rachitism and bone anomalies seen in newborn are evaluated as a result of pharmacodynamic effect.

In people working in magnesium melting workshops, “metal fume fever” is observed as a result of inhalation of magnesium vapor. Symptoms include fever, shivering, nausea, vomiting and muscle pain. This situation is benign. It lefts no permanent damage.

**6. PHARMACEUTICAL PROPERTIES**

**6.1. List of excipients**

Sodium chloride

Water for injection

**6.2. Incompatibilities**

Magnesium sulphate is incompatible with alkali hydroxides (the insoluble magnesium hydroxide is formed), alkali carbonates (the insoluble magnesium carbonate is formed) and salicylates. Magnesium ions inhibit the activity of streptomycin sulphate and tetramycin sulphate.

**6.3. Shelf life**

24 month.

**6.4. Special precautions for storage**

Store at room temperature under 25°C, away from the light.

**6.5. Nature and contents of package**

100 ml PP (Polypropylene) bag at form of without kit.

**6.6 Special precautions for disposal and the residue from medicinal products**

Do not throw away any expired or unused medicines! Give to the collection system determined by the Ministry of Environment and Urbanization.

**7. MARKETING AUTHORISATION HOLDER**

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**8. MARKETING AUTHORISATION NUMBER**

2017/901

**9. OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 06.12.2017
Date of latest renewal:

**10. DATE OF REVISION OF THE SPC**

03.12.2019