SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG
Aminophylline S.A.L.F. 240 mg/10 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1ml of solution contains:
Theophylline Ethylenediamine dihydrate 24 mg (equivalent to of Theophylline Ethylenediamine (Aminophylline) 22.1 mg).

Each ampoule of 10ml contains:
240 mg of Theophylline Ethylenediamine dihydrate equivalent to 221 mg Theophylline Ethylenediamine (Aminophylline).

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

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear, slightly yellow solution.

4. CLINICAL INFORMATION
4.1. Therapeutic indications
- Bronchial asthma.
- Pulmonary affections with bronchial spastic component.

4.2. Posology and method of administration
Adults
The treatment is reserved to severe cases of bronchial asthma through a slow infusion of a solution obtained by diluting 480 mg of Aminophylline (equal to 2 ampoules of Aminophylline S.A.L.F. 240 mg/10 ml) in 50 ml of a compatible solution for infusion (e.g. saline solution, glucose solution).
The infusion rate of the solution should not exceed 3.6 ml/min (equal to 25 mg of Aminophylline/minute).
The total administered dose should not exceed 0.8 ml/kg (equal to 5.6 mg of Aminophylline/kg).
This infusion can be followed by another maintenance infusion obtained by diluting 240 mg of Aminophylline (equal to 1 ampoule of Aminophylline S.A.L.F. 240 mg/10 ml) in 500 ml of a solution for infusion (see above).
The infusion rate for the maintenance solution should be:
- 1.9 ml/kg/hour (equal to 0.9 mg of Aminophylline/kg/hour) in smoking adults below 50 years.
- 0.9 ml/kg/hour (equal to 0.45 mg/kg/hour) in no smoking adults below 50 years.
- 0.5 ml/kg/hour (equal to 0.25 mg/kg/hour) in adults with heart failure or hepatic impairment.

In any case, the intravenous administration of the product should be carried out with the patient in supine position, at a controlled slow rate (15-20 minutes).

Children
The dosage in children below 9 years is 1 mg/kg/hour.

Do not use the solution in presence of crystallization.
Inject slowly.

4.3. Contraindications
Known hypersensitivity to the active ingredients, to other xanthine derivatives or to any of the excipients. Acute myocardial infarction, hypotensive states, lactation (see section 4.6).

4.4. Special warnings and precautions for use
The solution should be a clear, slightly yellow solution and free of visible particles.
It is intended for a single, uninterrupted administration and any residue should be discarded.
Aminophylline should not be administered simultaneously with other xanthine preparations.
Caution is also required when associating Aminophylline with ephedrine or other sympathomimetic bronchodilator drugs.
Phenytoin, other anticonvulsants and the smoke of cigarettes may increase the clearance of Aminophylline thus reducing its plasmatic half-life. In such cases it may be necessary to increase the dosage of Aminophylline.
The product should be administered with caution in the elderly, in patients with cardiopathies, hypertension, with severe hypoxemia, hyperthyroidism, chronic pulmonary heart disease, congestive heart failure, peptic ulcer and in patients with severe renal and hepatic affections.
Extreme caution is recommended when administering Aminophylline in children.
Various factors can reduce the hepatic clearance of Aminophylline with consequent increase of the plasmatic levels of the drug. Among these are included age (newborns and premature infants under 1 year of age, the elderly over sixty years who have a reduced clearance), congestive heart failure, chronic obstructive lung affections and related infections, fever (a temperature of 39°C or higher for 24 hours or more, or a lower temperature but for longer periods), hypothyroidism, liver disease (cirrhosis, acute hepatitis), acute pulmonary edema, sepsis, shock, and the concomitant administration of certain drugs (see section 4.5 "Interaction with other medicinal products and other forms of interaction"). In the presence of these factors, it is recommended to monitor blood levels of Aminophylline considering that its therapeutic values are 10-15 µg/ml and the minimum toxic dose 20 µg/ml.

Important information about some of the ingredients:
None.

4.5. Interaction with other medicinal products and other forms of interaction
Drugs that may decrease the hematic concentration of Aminophylline and consequently reduce its effectiveness: adenosine, barbiturates, butalbital, cannabis, carbamazepine, felodipine, phenytoin, phenobarbital, smoke of cigarette, furosemide, hypericum, isoniazid, nifedipine, pancuronium, primidone, rifampicin, rifapentine, ritonavir, sulfinpyrazone, terbutaline.

Drugs that may increase the hematic concentration of aminophylline and consequently increase its toxicity': pipemidic acid, albendazole, allopurinol, amiodarone, anagrelide, bupropion, cimetidine, clarithromicyn, clindamycin, oral contraceptives, diltiazem, disulfiram, enoxacin, erythromycin, fluoroquinolones, fluvoxamine, furosemide, imipenem, interferons (alpha-2a, alpha-2b), ipriflavone, isoniazid, josamycin, lincomycin, macrolides, metotrexate, mexiletine, nifedipine, paroxetine, peginterferon alpha-2a, pentoxifylline,

propafenone, propanolol, ranitidine, riluzole, rofecoxib, telitromycin, oral anticoagulant therapy, ticlopidine, troleandomycin, anti-flu vaccine, verapamil.
The interaction between Isoproterenol (or Isoprenaline) and Aminophylline has not been clarified: in some cases, it was observed that Isoproterenol increases the clearance of Aminophylline with a consequent decrease of Aminophylline plasmatic concentrations.
Aminophylline increases the excretion of lithium carbonate and reduces its hematic concentration; it may modify the sensitivity and toxicity of the digitalis derivatives and the sympathomimetic ammines. It increases the hematic levels of ropivacaine and tacrolimus.
The simultaneous administration of Aminophylline and the following drugs increases toxicity: halothane (increase of cardiac toxicity), epinephrine (increase of toxicity in the central nervous system and gastrointestinal tract), ketamine (decrease of the seizure threshold).
Aminophylline decreases the effect of the benzodiazepines.
The plasmatic concentrations of Aminophylline may be reduced by the simultaneous administration of preparations with Hypericum perforatum that interfere with the enzymes responsible for the metabolism of the drugs and, consequently, should not be administered together with Aminophylline. The induction effect may persist for at least 2 weeks after suspension of the treatment with products containing Hypericum perforatum.
If a patient is treated contemporarily also with products containing Hypericum perforatum, the plasmatic levels of Aminophylline should be monitored and the therapy with Hypericum perforatum should be discontinued. In this case the plasmatic levels of Aminophylline may increase, and the dosage of Aminophylline might require an adjustment.

4.6. Pregnancy and lactation
Pregnancy
Though no negative effects of Aminophylline on the development of the fetus have been reported, the use of Aminophylline during pregnancy should be limited to the cases in which asthma represents a serious danger for the mother.
Lactation
Lactation is not compatible with administration of Aminophylline.

4.7. Effects on ability to drive and use machines
Aminophylline does not alter the capacity to drive or to use machinery.

4.8. Side effects
Here below are the possible side effects of Aminophylline organized according to MedDRA system organ classification. There are insufficient data to determine the frequency of each listed effect.

Cardiac disorders
Atrial fibrillation
Bradyarrhythmia in case of a rapid administration
Cardiac arrest Palpitations Syncopation
Tachyarrhythmia

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome

Metabolism and nutrition disorders
Increased urinary excretion of free cortisol
Decreased levels of triiodothyronine
Hypoproteinemia
Increased blood glucose
Increased levels of uric acid Lipid disorders

Nervous system disorders
Headache
Tremors
Sleeplessness
Intracranial hemorrhage
Dizziness
Seizures
Stuttering

Psychiatric disorders
Irritability
Trough
Anxiety
Restlessness

Renal and urinary disorders
Increased diuresis

4.9. Overdose
The first symptoms of overdose are represented by agitation, tremor, confusion, vomiting and tachycardia, followed by hematemesis, convulsions, cardiac arrhythmia and fever. First signs of intoxication are generalized tonic-clonic seizures and severe ventricular arrhythmia.
In case of overdose, diazepam should be administered against the toxic effects on the central nervous system.
An adequate respiratory assistance should also be available and the patient should be hydrated and his blood pressure monitored.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for systemic use in airway obstructive syndromes.
ATC code: R03DA05
Aminophylline is a medicinal combination of theophylline with ethylenediamine and it is much more soluble in water than theophylline.
It is therefore particularly suitable for parenteral administration.
The pharmacological properties of the product are therefore entirely attributable to theophylline, whose activity is mainly related to the intracellular cyclic AMP increase, induced by the inactivation of the phosphodiesterase enzyme. The cyclic AMP increase is directly related to the spasmolytic activity on the bronchial smooth muscle.

The resulting improvement of the respiratory function also depends on the intense stimulation of the respiratory bulbar center, which leads to an increase in the rate and the extent of the respiratory excursions. More recently, several experimental and clinical investigations have shown that theophylline has the ability to also perform an inhibiting action on the activation of the microtubular mast cell apparatus, by inhibiting or reducing the release of chemical mediators (histamine). As regards haemodynamics, Aminophylline reduces the systemic and pulmonary blood pressure and exerts positive chronotropic and inotropic effects, which result in an increase in the cardiac output. The increased cardiac work involves an increase in myocardial metabolic demands, usually offset by an increase in coronary flow.
Aminophylline exerts a diuretic effect, due to the increase in the renal blood flow and the action in the renal tubule.

5.2. Pharmacokinetic properties
The administration of Aminophylline causes a rapid and complete distribution of theophylline in the different body areas.

Distribution
Volume of distribution: 450 ml/kg.
Protein binding: about 40% in adults. Newborns have twice the amount of free theophylline compared to adults. The amount of theophylline not bound to plasma proteins decreases with age, in children over 10 years this difference is no longer present.

Metabolism
Theophylline in adults is primarily metabolized in the liver by cytochrome P4501A2.

Elimination
Theophylline is excreted in the kidneys: in adults 10-13% in newborns 0 to 3 months of age to 50%. The half-life of approximately 4 hours in children, in adults increases up to 6.9 hours.

5.3. Preclinical safety data
Chronic toxicity: Aminophylline up to 100 mg/kg/day has been well tolerated with an oral treatment prolonged for 6 months in rats and dogs: in fact, no changes dependent on the treatment have been highlighted in the blood and major organs. The administration of Aminophylline in some animals can cause a hypersensitivity to ethylenediamine, while toxic doses cause hyperexcitability, tachypnea, and sometimes convulsions.

6. PHARMACEUTICAL INFORMATION
6.1. List of the excipients:
Water for injections.

6.2. Incompatibility
Acidic solutions: Aminophylline is incompatible with strongly acidic solutions (formation of a precipitate).
An incompatibility has been detected between Aminophylline and the following solutions:
- Fructose 10% in saline solution,
- Invert sugar 10%,
- Invert sugar 10% in saline solution,

and also with:
amiodarone hydrochloride, ampicillin, bleomycin sulfate, calcium hydrochloride, cefazolin, cefotaxime, chlorpromazine, codeine phosphate, daunorubicin, doxorubicin, epinephrine, erythromycin gluceptate, insulin, isoproterenol hydrochloride, methadone, morphine, ondansetron, oxytocin, papaverine, phenytoin, promazine, promethazine, warfarin, sulfamethoxazole / trimethoprim.
This medicinal product must not be mixed with any other medicinal product except those mentioned in section 6.6.

6.3. Shelf life
The expiry date of the product is indicated on the packaging materials.
For shelf life after dilution see clause 6.6.

6.4. Special precautions for storage
Store in the original package to protect from light.
Store below 25°C.

6.5. Nature and capacity of the container
Yellow Type I glass ampoule.
Each pack contains 5 ampoules of 10 ml solution.

6.6. Special precautions for disposal and other handling
Aminophylline S.A.L.F. 240 mg/10 ml must be diluted prior to use with one of the following:
- Sodium Chloride 0.9% Solution
- Glucose 5% Solution

According to these volumes, in compliance with executed compatibility tests:
480 mg of Aminophylline S.A.L.F. 240 mg/10 ml (equal to 2 ampoules of 240 mg/10 ml) in 50 ml of sodium chloride 0.9% or glucose 5%.

OR

240 mg of Aminophylline S.A.L.F. 240 mg/10 ml (equal to 1 ampoules of 240 mg/10 ml)
should be diluted in 500 ml of Sodium chloride 0.9% or glucose 5%.

In case of dilution:
Chemical stability has been proven for 8 hours in 25°C (with sodium chloride 0.9% or glucose 5%).
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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

7. MARKETING AUTHORIZATION NUMBER(S)
158-55-34846-00

8. MARKETING AUTHORIZATION HOLDER and Importer
RAZ PHARMACEUTICS LTD, ISRAEL
31 Gesher Haetz, Industrial Park, Emek Hefer, Israel

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