PACKAGE LEAFLET

NOVPHYLLIN

ATC code: R03DA05

PHARMACOTHERAPEUTIC GROUP:

Anti-asthmatic medicines. Xanthines.

COMPOSITION:

Aminophylline anhydrous 100 mg in one film-tablet and 350 mg in one retard tablet.

ACTION:

Aminophylline is a compound of theophylline with etylendiamine which improves its solubility and absorbtion. It acts as a bronchodilator through relaxation of the bronchial smooth muscles and also as a peripheral vasodilator: it dilates the vessels of the heart (it augments oxygen consummation), the brain, the kidneys. It possesses a moderate diuretic effect. It inhibits the thrombocyte aggregation. It stimulates the respiratory centre, it enhances the frequency and the power of the heart contractility. It stops the night reduction of the forced respiratory volume; it enhances the collateral pulmonary ventilation; it improves the function of the respiratory muscles and the mucocilliary clearance. It diminishes the hyper-reactivity of the organism, it increases the number and the activity of the T suppressory cells in the peripheral blood. The exact mode of activity is not fully settled. The effect on the bronchial muscles and the pulmonary blood vessels is realised by inhibition of specific phosphodiesterases that leads to reduced detachment and to accumulation of intracellular cyclic 3,5-AMP.
Aminophylline in the organism immediately releases theophylline and consequently the kinetics follows that of theophylline. It is rapidly and entirely absorbed. The speed but not the degree of resorption is diminished by food. Peak plasma concentrations are reached 2-3 hours after its peroral reception. About 60% is bound to plasma proteins, but in new-borns and in geriatric patients that part is 40%. It is metabolised in the liver. It has large interindividual differences in the speed of the hepatic metabolism which interferes the clearance, the plasma concentrations and the biological half-life. The liver metabolism is influenced widely by age, smoking, alcohol, different diseases' diet and drug interactions. The biological half-life in children ranges from 1 to 9 hours (mean value 3,7) and in adult non-smokers - from 3 to 15 hours (mean value 7,7). In smokers the half-life is shorter. It is longer in kidney diseases, in prematurely born infants, in adults with respiratory diseases, in heart failure, liver damages, chronic alcoholism, high temperature, adults over 55 years of age. Higher serum concentrations are reached in mornings' reception but not in the evenings, probably because of slighter night absorption. In adults about 10% of theophylline are excreted via kidneys unchanged but in new-borns it is about 50%. It is distributed equally in all the tissues. It passes via placenta and is excreted in the milk.

Mean peak plasma concentrations in the sustained release form are reached in 6,25 hours at a value of 5,26 mcg/ml.

**INDICATIONS:**

For interruption of broncho-obstructive syndrome in bronchial asthma and in chronic obstructive pulmopathies; in the combined therapy of chronic heart failure and disturbances of the cerebral blood flow.
CONTRAINDICATIONS:
Hypersensitivity to the preparation or to theophylline; acute pulmonary oedema; acute myocardial infarction; acute gastritis or active peptic ulcer; epilepsy (it can decrease the seizure threshold); tachyarrhythmias.

ADVERSE REACTIONS/SIDE EFFECTS:
The adverse reactions are more frequent in prolonged chronic reception than following a single high dose. They are more frequent in geriatric patients and when high doses have been used. The serum concentration should not exceed 20 mcg/ml.

Slighter reactions are: rashes, abdominal pain, anxiety, desorientation or behavioural disturbances, diarrhoea, hematemesis, hypotension. As a result of provoked hypoglycaemia and hypokalemia are: tremor, continuing vomiting.

More serious reactions are: sinus tachycardia, ventricular arrhythmia, gastroesophageal reflux (epigastral discomfort, vomiting), rarely are: seizures, dermatitis. The manifestation of seizures is a sign for intoxication; in children it may be the first sign for overdosage.

The complaints which last longer or disturb the patient are: headache, polyuria, insomnia, nausea, anxiety, tachycardia, tremor. Those symptoms occur when the therapeutic concentrations are reached quickly.

DRUG AND NON-DRUG INTERACTIONS:
Nophylline should be carefully applied with anticoagulants, with other theophyllines or purine derivatives. The clearance of theophylline is decreased (clinical significance has clearance changes at a range of 25%) by alcohol, allopurinol, cimetidine, estrogen containing contraceptives, disulfiram, ciprofloxacin, erythromycin and most of the macrolides, methotrexate, mexiletine, propafenone, pentoxiphylline, propranolol,
tacrine, thiabendazole, ticlopidine, verapamil. Drugs which increase the clearance of theophylline are: aminoglutethimide, carbamazepine, isoproterenol, phenobarbital, phenytoin, rifampicin.

Novphyllin antagonises the cardiovascular effects of adenosine. It inverts the sedative effect of benzodiazepines and antagonises the bronchospasmodic effect of β-blockers. The symptoms such as: nausea, anxiety, insomnia, are potentiated by ephedrine. Together with halothane can provoke arrhythmia. It antagonises the blockading effect of non-depolarising neuromuscular blockers. Together with ketamin it decreases the seizure threshold.

Low protein and highly carbohydrate diet decrease the theophylline clearance with about 25% and highly protein and low carbohydrate diet increase it with about 25%. The active and passive tobacco smokers have increased clearance and decreased serum levels. Highly doses of chocolate, cocoa, tea, coffee, coca cola, can increase the stimulating effect of novphyllin on the central nervous system.

**PRECAUTIONS AND WARNINGS:**

Novphyllin is a preparation with a narrow therapeutic width and varying individual metabolism that predisposes possibility for intoxication. Signs for adverse reactions should be carefully estimated: abdominal pains, vomiting, desorientation, tachycardia, seizures (which are signs for oncoming intoxication).

It should be carefully administered in: febrile states, sepsis (the clearance of nophyllin is decreased); hypothyroidism; decompensated heart failure, heart coronary disease, active gastroduodenal ulcer.

Nophyllin changes the results of the tests for assessment of cholesterol, free cortisol excretion in the urine, free fatty acids, glucose, HDL and
HDL/LDL-ratio, uric acid. The values of those tests can be increased by the therapeutic serum concentrations of the preparation.

**PREGNANCY AND BREAST-FEEDING:**

It should be administered only after a serious estimation of the benefit and the risk for the pregnant woman, the foetus or the new-born. It inhibits slightly the uterine contractions. It passes via placenta. There are experimental data for embryotoxicity. It is excreted in the milk in 1% and provokes anxiety, accelerated heart activity and vomiting in the new-born.

**EFFECTS ON ACTIVE ATTENTION, DRIVING ABILITY AND OPERATION OF MACHINERY:**

There are not data about unfavourable effect on active attention, reflexes and motor activity.

**MODE OF ADMINISTRATION AND DOSAGE:**

The dosage is strongly individual and should be considered in connection with the therapeutic effect. It should start at a lower dose and reach a maintenance dose for up to several days.

The dosage intervals are individually specified, they range from 6 to 12 hours. The most appropriate interval for children and smokers is 6 hours; for adult non-smokers is 8 hours; for new-borns and patients with liver damages is 12 hours.

*Filmtablets of 100 mg:*

The initial daily dose in adult non-smoker patients is 5 mg/kg and maintenance daily dose of 9,6 mg/kg, divided in 3 receptions every 8 hour. For smokers and patients with heart failure, cor pulmonale and liver diseases an individual assessment of the dose is needed.
The initial dose in children is 5 mg/kg and the maintenance dose is 15 mg/kg daily divided in intervals of 6 to 12 hours.

**Sustained release tablets of 350 mg:**

They are administered 1 tablet 2 times per day every 12 hour together with a cup of water 30 to 60 minutes before meal or 2 hours after meal. Tablets should not be chewed or broken to pieces.

**OVERDOSAGE:**

Overdosage is often seen because of the low therapeutic index. Usually symptoms of overdosage occur in serum concentrations over the upper therapeutic limit of 20 mcg/ml but in some patients those signs occur in lower serum concentrations. The signs of overdosage can begin with abdominal pains, anxiety, desorientation, diarrhoea, hematemeses, hypokalemia, hypotension, hypertermia, metabolite acidosis, seizures, tachyarrhythmia, tachycardia, prolonged tremor, vomiting. The overdosage could immediately express itself with serious symptoms: mainly development of arrhythmias, seizures. Patients with seizures might suffer of hypoxia, acidosis, rhabdomyolysis, myoglobin kidney failure.

Treatment: activated charcoal in order to discontinue the enteroenteral recirculation of aminophylline. Gastric lavage is not needed if the patient has vomited. Intensive treatment if needed - in specialised department.

**DOSAGE FORM AND PACKAGES:**

20 film-tablets of 100 mg in one package.

20 sustained release tablets of 350 mg in one package.

**STORAGE:**

In a dry and protected from light place at a temperature of 15-25°C.