

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zepholin S.R. 200 mg Prolonged Release Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of Theophylline.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsules, hard.

Size 2, green opaque cap and green transparent body, printed ‘TH 200’ in white on both cap and body, containing white pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the symptomatic or prophylactic relief of bronchospasm associated with asthma, chronic bronchitis and emphysema. Zepholin should not be used as first drug of choice in the treatment of asthma in children.

4.2 Posology and method of administration

For oral use only. The capsules should be swallowed whole, after meals with plenty of fluid. The treatment should begin in the evening shortly before bed and should be increased slowly over 2-3 days. The daily dose should be divided between morning at breakfast and evening, shortly before bed. Duration of use is dependent on the severity of the condition.

Adults:

Recommended dose scheme:

Age in years	Body weight in kg ¹⁾	mg Theophylline/kg/day	mg Theophylline/day
Adults Non-smokers	60 - 70	11 - 13	660 – 910
Adults Smokers	60 - 70	18	1080 – 1260

¹⁾: in the case of adipose patients the normal weight should be taken.

An individual dosing scheme can be worked out on the basis of the theophylline serum profiles.

Children:

Children under 6 months:
Zepholin should not be used in children under 6 months of age.

Children under 6 years:
Zepholin capsules should not be used in children under 6 years of age. Other dosage forms are available that are more suitable for children aged less than 6 years.

Children from 6 years of age should be treated according to their body weight with Zepholin 100 mg or 200 mg.

Age in years	Body weight in kg ¹⁾	mg Theophylline/kg/day	mg Theophylline/day
6 - 8	20 - 25	24	480 - 600
8 - 12	25 - 40	20	500 – 800
Adolescents 12 - 16	40 – 60	18	720 – 1080

¹⁾: in the case of adipose patients the normal weight should be taken.

- Theophylline should be dosed individually according to the efficacy. Each patient should be titrated to a suitable dosage regimen (plasma theophylline level 5 – 12 µg / ml) by clinical assessment. The plasma theophylline levels should be monitored especially if the efficacy is insufficient or if undesirable effects occur.
- To determine the initial dose, a possible pre-medication with theophylline or its compounds should be considered with regard to a dose reduction.
- Since theophylline is not absorbed by fatty tissues, it is recommended to take the normal weight for determination of the dose.
- Smokers need a higher theophylline dosage corresponding to the body weight, because the theophylline clearance is higher than in non-smokers. Smokers, who stop smoking, should be treated carefully because of the rise of the plasma theophylline level.
- Theophylline clearance is reduced in patients with cardiac insufficiency, oxygen deficiency, pneumonia, viral infection (especially influenza) and in patients who are treated with other medicinal products (please refer to chapter 4.5 “Interactions with other medicinal products”). Furthermore, the Theophylline clearance may be reduced after an influenza- and BCG vaccination. A reduction of the dosage may be necessary in these patients.
- Theophylline clearance is often reduced in patients with an impaired liver function. In patients with severe renal dysfunction, an accumulation of the theophylline metabolites may occur. Such patients need reduced dosages and an increase of the dosage should occur with special care.
- Children older than 6 months need a higher theophylline dosage than adults who don’t smoke, because the theophylline clearance is higher in these patients. In contrast, the theophylline clearance is reduced in babies younger than 6 months.
- The theophylline clearance is decelerated in elderly patients (over age 60).

4.3 Contraindications

- Use in patients with known hypersensitivity to the xanthine group of drugs or to any of the excipients listed in section 6.1
- Recent myocardial infarction
- Acute tachycardiac arrhythmia
- Children under 6 months of age.

4.4 Special warnings and precautions for use

Zepholin should be used only when strictly indicated and cautiously in patients with:

- unstable angina pectoris
- tendency to suffer from tachycardiac arrhythmia
- severe hypertension
- hypertrophic obstructive cardiac myopathy
- hyperthyroidism
- seizure
- gastric and/or duodenal ulcer
- porphyria
- severe hepatic or renal impairment
- alcohol consumption

Caution should be exercised in elderly males with pre-existing partial outflow obstruction, such as prostatic enlargement, due to the risk of urinary retention.

The use of Zepholin in old, polymorbid, critically ill and / or intensive medically treated patients is associated with an increased risk for intoxication and should therefore be controlled by therapeutic drug monitoring (TDM). In patients receiving electroconvulsive therapy, caution should be exercised as Zepholin may prolong seizures. The occurrence of a status epilepticus is possible.

Care should be taken in its use in patients suffering from insomnia.

It is not possible to ensure bioequivalence between different prolonged release theophylline products. Therefore, patients once titrated to an effective dose, should not be changed from Zepholin preparations to any other slow or prolonged release xanthine preparations without re-titration and clinical assessment.

Where patients are taking more than 1000 mg of theophylline daily, regular measurement of theophylline levels is mandatory.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) should not be used while taking Zepholin due to the risk of decreased plasma concentrations and reduced clinical effects of Zepholin. (See 4.5 Interactions).

In case of insufficient effect of the recommended dose and in case of adverse events, Zepholin plasma concentration should be monitored

Acute febrile illness:

Fever decreases the clearance of Zepholin. It may be necessary to decrease the dose to avoid intoxication.

4.5 Interaction with other medicinal products and other forms of interaction

Zepholin is metabolized in the liver by the enzyme CYP1A2. The concomitant use of drugs that affect this enzyme may lead to changes in theophylline clearance.

Zepholin acts synergistically with other medicines containing xanthines, beta-sympathomimetics, caffeine and similar substances.

An accelerated degradation of theophylline and / or decreased bioavailability as well as reduced efficacy can be found:

- in smokers
- during concomitant treatment with barbiturates (particularly phenols, or pentobarbital), carbamazepine, phenytoin, rifampicin, primidone, sulfinpyrazone, ritonavir, hypericum perforatum and aminoglutethimide.

Theophylline levels should be monitored in case of concomitant treatment with these drugs and dose adjustment should be performed if necessary, even after the discontinuation of these medications.

Delayed degradation and / or increased theophylline blood levels with an increased risk of overdose and increased risk of side effects may occur during concomitant treatment with the following drugs: oral contraceptives, macrolide antibiotics (eg: erythromycin, clarithromycin, josamycin, spiramycin), quinolones (gyrase inhibitors), isonicotinic acid hydrazide, thiabendazole, calcium-channel blockers (eg diltiazem or verapamil), propranolol, propafenone, mexiletine, ticlopidine, cimetidine, allopurinol, α -interferon, rofecoxib, pentoxifylline, fluvoxamine, viloxazine, disulfiram, zileuton, phenylpropanolamine, influenza- and BCG-vaccines. A dose reduction of Zepholin may be indicated.

According to single reports, symptoms of theophylline overdose were observed during concomitant treatment with ranitidine, aciclovir or zafirlukast. When used concomitantly, the required individual theophylline dose should be determined carefully.

The dose of Zepholin should be reduced during concomitant treatment with

- ciprofloxacin to a maximum of 60%,
- enoxacin to a maximum of 30% and
- grepafloxacin or clinafloxacin to 50% of the recommended dose.

Other quinolones (eg. pefloxacin, pipemidic acid) can increase the effect of Zepholin. It is strongly recommended to monitor the theophylline concentration during concomitant treatment with quinolones closely.

The theophylline concentration may rise or fall during concomitant treatment with isoniazid. Monitoring of the plasma theophylline level is indicated.

During concomitant treatment with lithium, decrease in serum lithium level should be expected, but its magnitude cannot be predicted. Monitoring of lithium levels at 3 or 4 days after adding theophylline to assess initial degree and direction of serum level change and again at steady state (time will vary with lithium clearance) will allow adjustment of lithium dose. Even when theophylline is discontinued, close monitoring of lithium levels is again important. Here, one would predict a rise in serum lithium levels due to decreased lithium clearance.

The effect of β -blockers, adenosine and benzodiazepines can be reduced by the simultaneous administration of theophylline.

Zepholin enhances the diuretic effect of diuretics.

There is evidence that lowering the seizure threshold may occur in the brain during concomitant administration of certain fluoroquinolones or imipenem.

The use of halothane may lead to serious cardiac arrhythmia in patients who receive Zepholin.

The effect of corticosteroids on the theophylline kinetics is not yet conclusive.

Due to the various interactions of theophylline, serum level controls are generally advisable on long-term use of theophylline together with other drugs.

Plasma concentrations of theophylline can be reduced by concomitant use of the herbal preparation St. John's Wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes by St. John's Wort. Herbal preparations containing St. John's Wort should therefore not be combined with Zepholin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's Wort. If the patient is already taking St. John's Wort check theophylline levels and stop St. John's Wort. Theophylline levels may increase on stopping St. John's Wort. The dose of theophylline may need adjusting.

4.6 Fertility, pregnancy and lactation

Pregnancy

Currently, there are insufficient data for an application of Zepholin during the first trimester of pregnancy. Therefore, a treatment with Zepholin should be avoided during this time.

During the second and third trimester, Zepholin should be used only after a strict benefit-risk assessment, as it crosses the placenta and can have a sympathomimetic effect on the foetus.

With increasing duration of pregnancy the plasma protein binding and clearance of theophylline may decrease. A dose reduction may be necessary to avoid adverse effects.

A treatment with Zepholin at the end of pregnancy may lead to the inhibition of uterine contractions. Prenatally exposed newborns need to be carefully monitored for theophylline effects.

Lactation

Theophylline is excreted in breast milk; therapeutic serum concentrations can be achieved in the child. For this reason, the therapeutic dose of Zepholin to a nursing woman should be kept as low as possible. Breast-feeding should take place immediately prior to administration of the drug.

The breastfed baby needs to be monitored carefully for the possible occurrence of theophylline -effects. If higher therapeutic doses should be required, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

Zepholin has moderate influence on the ability to drive and use machines as it may change the ability to react. The ability to actively participate in road traffic, using machines or to work at height and without a firm grip may be impaired. This applies even more in combination with alcohol or medicinal products, which affect the ability to react.

4.8 Undesirable effects

The following categories are used as a basis for evaluating undesirable effects:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

	Common	Uncommon	Not known
Immune system disorders		Hypersensitivity reactions to theophylline (e.g. rash, pruritus, urticaria, bronchospasm) including anaphylactic and anaphylactoid reactions.	
Metabolism and nutrition disorders		Hyperuricaemia	Changes in serum electrolytes, especially hypokalaemia increase of serum calcium and creatinine hyperglycaemia
Nervous system disorders	Headache	Convulsion Anxiety Tremor Seizures Dizziness	Agitation Restlessness Insomnia
Cardiac disorders		Atrial tachycardia Palpitations Sinus tachycardia Tachycardia Palpitations	Arrhythmia Drop in blood pressure
Gastrointestinal disorders	Nausea	Abdominal pain Diarrhoea Gastric irritation Gastro-oesophageal reflux Vomiting	Gastrointestinal discomfort stimulation of the secretion of gastric acid
Skin and subcutaneous tissue		Pruritus Rash	
Renal and urinary disorders		Diuresis Urinary retention	

More severe side effects can occur in individual hypersensitivity or an overdosage (Theophylline serum levels above 20 µg / ml) (please refer to 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

At serum Theophylline levels of 20-25 µg / ml the known adverse effects of Theophylline occur with increased intensity.

Especially in serum Theophylline levels higher than 25 µg / ml, toxic effects such as seizures, sudden drop in blood pressure, ventricular arrhythmias, cardiovascular failure, rhabdomyolysis and severe gastrointestinal symptoms (e.g. gastrointestinal bleeding) may occur. Such reactions can occur even without former slighter side effects. Children in particular are sensitive to Theophylline overdosage.

Warning: serious features may develop as long as 12 hours after overdosage with sustained release formulations. With increased individual sensitivity, symptoms of overdosage are possible even below the above mentioned serum concentrations.

Therapeutic measures

- *In slight overdose symptoms:*

The corresponding drug should be discontinued and the serum Theophylline levels should be measured. For restart of treatment, the dose should be reduced accordingly.

- *Treatment of all intoxications with Theophylline:*

Up to two hours after ingestion, gastric lavage may be useful. To further poison removal, activated charcoal optionally in combination with a rapidly acting laxative (e.g. Galuber's salt) should be administered repeatedly. Measure the plasma potassium concentration urgently, repeat frequently and correct hypokalaemia.

- *In central nervous system disorders (eg. restlessness, and convulsions):*

Diazepam i.v., 0.1 - 0.3 mg / kg body weight, up to 15 mg

- *When life threatening:*

Monitoring of vital functions,
Maintain the airways (intubation),

Supply of oxygen,

if needed: i.v. fluid substitution with plasma expanders,

Check and possibly correct the water and electrolyte balance,

Hemoperfusion (see below).

- *In threatening cardiac rhythm disorders:*

i.v. administration of propranolol in non-asthmatics (1 mg in adults, 0.02 mg / kg in children), this dose may be repeated every 5-10 minutes until the rhythm normalization or until the maximum dose of 0.1 mg / kg.

- *Caution:*

Propranolol may cause severe bronchospasm in asthmatic patients. Verapamil should therefore be administered in patients with asthma.

Particularly in severe intoxications, where a response to the measures mentioned above is not sufficient, as well as at very high serum levels of Theophylline, a rapid and complete detoxification can be achieved by hemoperfusion or hemodialysis. In general this can be refrained, as Theophylline is metabolized quickly enough.

Further treatment of poisoning with Theophylline is dependent on the extent, the course and the present symptoms.

- *Extracorporeal methods of reducing the serum Theophylline:*

The serum concentrations may rapidly decrease by increasing the clearance of Theophylline with extracorporeal methods. Hemoperfusion with activated charcoal is the most effective method, where the clearance of Theophylline rises to 6-fold, albeit serious complications such as hypotension, hypocalcemia, decreased platelet count and haemorrhage may occur. Hemodialysis is effective as the administration of multiple doses activated charcoal and has a lower risk for serious complications than hemoperfusion with charcoal.

The serum Theophylline may rise again to 5 to 10 µg / ml due to the redistribution of Theophylline from the tissue after completion of hemoperfusion with activated charcoal or hemodialysis.

In the treatment of ventricular arrhythmias, proconvulsant antiarrhythmic agents such as lignocaine (lidocaine) should be avoided because of the risk of causing or exacerbating seizures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A xanthine derivative competitively inhibits phosphodiesterase, increasing intracellular CAMP concentrations.

5.2 Pharmacokinetic properties

Serum half life is about 12 hours. Effective plasma concentrations: 5-12 µg/ml (do not exceed 20 µg/ml). Zepholin is mainly excreted by the kidneys.

5.3 Preclinical safety data

Theophylline is a well established product and a large number of studies have been carried out in animals. The oral LD50 of theophylline in mice is 350 mg/kg. In humans, adverse reactions often occur when serum theophylline levels exceed 20 µg/ml.

Long term reproductive studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or the effect on fertility of theophylline preparations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone

Colloidal anhydrous silica

Ammonio Methacrylate Copolymer (Type B)

Ammonio Methacrylate Copolymer (Type A)

Triethylcitrate (TEC)

Talc

Capsule Shell:

Gelatin

Indigotine (E132)

Titanium dioxide (E171)

Printing ink:

Shellac

Titanium dioxide (E171)

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: Five years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister (Aluminium/PVC)

Pack size: 56 capsules.

14 capsules per strip, 4 strips per pack.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Astellas Pharma Co. Ltd.

5 Waterside

Citywest Business Park

Naas Road

Dublin 24

Ireland

8 MARKETING AUTHORISATION NUMBER

PA1241/015/002

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