# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

UNIPHYLLIN Continus 300 mg Prolonged-Release Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Theophylline 300 mg as Theophylline Monohydrate

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, capsule-shaped tablet, plain on one side and ‘U300’ on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

In the treatment and prophylaxis of bronchospasm and inflammation associated with asthma, chronic bronchitis and emphysema. Also indicated in adults for the treatment of cardiac asthma and left ventricular or congestive cardiac failure. Theophylline should not be used as first drug of choice in the treatment of asthma in children.

### 4.2 Posology and method of administration

Route of Administration
Oral.
The tablets should not be broken, crushed or chewed. Breaking, crushing or chewing the tablets may lead to a rapid release of theophylline with the potential for toxicity.

Asthma

*Adults and the elderly*

Patients should receive 200 mg 12-hourly.

In more severe cases, the dosage may be increased to 300 mg 12-hourly or 400 mg 12-hourly.

For asthmatic patients whose nocturnal symptoms are particularly troublesome, a higher dose at night may provide additional bronchodilator benefit.
*Children*
The usual maintenance dose is 200 mg 12-hourly but some children with chronic asthma require and tolerate much higher doses for which purpose UNIPHYLLIN CONTINUS tablets 300 mg may be prescribed.
UNIPHYLLIN CONTINUS tablets should not be used in children below 6 years of age. Other dosage forms are available that are more suitable for children aged less than 6 years.

Emphysema, chronic bronchitis, left ventricular failure and congestive cardiac failure
*Adults and the elderly*
The usual maintenance dose for patients 70 kg body weight or over: 400 mg 12-hourly following an initial week of therapy on 200 mg or 300 mg 12-hourly.
The usual maintenance dose for patients less than 70 kg body weight: 300 mg 12-hourly following an initial week of therapy on 200 mg 12-hourly.
A reduction of dosage may be necessary in the elderly patient.

Patients vary in their response to xanthines and it may be necessary to titrate dosage individually.

General considerations
At doses of 200 mg 12-hourly in adults it is not generally necessary to monitor plasma theophylline levels.
At higher doses in adults, in children and if drug interactions are suspected, patients should be monitored to ensure that plasma theophylline levels do not exceed 20 mcg/ml (20 mg/litre, 110 µMol/litre).

For patients not presently receiving theophylline whose night time symptoms persist despite other therapy, a single evening dose of UNIPHYLLIN CONTINUS tablets may be added to their regimen.

## 4.3 Contraindications

Use in patients with known hypersensitivity to the xanthine group of drugs or any of the excipients.
Theophylline should not be administered to children under 6 months of age.

## 4.4 Special warnings and precautions for use

1. Caution should be exercised in patients with cardiac disease. Severe side effects (cramps, convulsions, supraventricular tachycardia) may appear at very high serum concentrations, in which case medication should be discontinued.
2. Caution should be exercised in elderly males with pre-existing partial outflow obstruction, such as prostatic enlargement, due to the risk of urinary retention.
3. Care should be taken in patients suffering from insomnia.
4. Alternative treatment is advised for patients with a history of seizure activity.
5. 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 UNIPHYLLIN CONTINUS tablets preparations to other slow or prolonged release xanthine preparations without re-titration and clinical assessment.
6. Fever decreases the clearance of theophylline. It may be necessary to decrease the dose to avoid intoxication.
7. In case of insufficient effect of the recommended dose and in case of adverse events, theophylline plasma concentration should be monitored.

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

The following increase clearance and it may therefore be necessary to increase dosage to ensure a therapeutic effect: aminoglutethimide, carbamazepine, isoprenaline, moracizine, phenytoin, rifampicin, sulphinpyrazone, barbiturates and hypericum perforatum. Plasma concentrations of theophylline can be reduced by concomitant use of the herbal preparation St. John's Wort (hypericum perforatum). Smoking and alcohol consumption can also increase clearance of theophylline.

The following reduce clearance and a reduced dosage may therefore be necessary to avoid side-effects: allopurinol, carbimazole, cimetidine, ciprofloxacin, clarithromycin, diltiazem, disulfiram, erythromycin, fluconazole, interferon, isoniazid, methotrexate, mexiletine, nizatidine, norfloxacin, propafenone, propranolol, oxpentifylline, ofloxacin, thiabendazole, verapamil, viloxazine hydrochloride and oral contraceptives (see Section 4.9 Overdose). The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely.

Factors such as viral infections, liver disease and heart failure also reduce theophylline clearance (see Section 4.9 Overdose). There are conflicting reports concerning the potentiation of theophylline by influenza vaccine and physicians should be aware that interaction may occur. A reduction of dosage may also be necessary in elderly patients. Thyroid disease or associated treatment may alter theophylline plasma levels. There is also a pharmacological interaction with adenosine, benzodiazepines, halothane, lomustine and lithium and these drugs should be used with caution.

Care should be taken in its concomitant use with ß-adrenergic agonists, glucagon and other xanthine drugs, as these

will potentiate the effects of theophylline. The incidence of toxic effects may be enhanced by the concomitant use of ephedrine.

The hypokalaemia resulting from ß2 agonist therapy, steroids, diuretics and hypoxia may be potentiated by xanthines. Particular care is advised in patients suffering from severe asthma who require hospitalisation. It is recommended that serum levels are monitored in such situations. Theophylline may decrease steady state phenytoin levels.

## 4.6 Fertility, pregnancy and lactation

There are no adequate data from well controlled studies of the use of theophylline in pregnant women. Theophylline has been reported to give rise to teratogenic effects in mice, rats and rabbits (See section 5.3). The potential risk for humans is unknown. Theophylline should not be administered during pregnancy unless considered essential by the physician. Theophylline is secreted in breast milk, and may be associated with irritability in the infant, therefore it should only be given to breast feeding women when the anticipated benefits outweigh the risk to the child.

## 4.7 Effects on ability to drive and use machines

No known effects.

## 4.8 Undesirable effects

The side effects are listed below. In most cases they disappear by reduction of the dose. If side effects appear, serum theophylline levels should be monitored and maintained between 10 and 15 µg/ml (see Section 4.9 Overdose).

The adverse drug reactions (ADRs) listed below are classified by body system according to their incidence (common or uncommon). Common ADRs have an incidence of ≥ 1% and uncommon ADRs have an incidence of < 1%.

| **Undesirable effects** | **Common (≥ 1%)** | **Uncommon (< 1%)** |
|---|---|---|
| **Immune system disorders** | | Anaphylactic reaction |
| | | Anaphylactoid reaction |
| | | Hypersensitivity |
| | | |
| **Metabolism and nutrition disorders** | | Hyperuricaemia |
| | | |
| **Psychiatric disorders** | | Agitation |
| | | Anxiety |
| | | Insomnia |
| | | |
| **Nervous system disorders** | Headache | Convulsion |
| | | Dizziness |
| | | Tremor |
| | | |
| **Cardiac disorders** | | Atrial tachycardia |
| | | Palpitations |
| | | Sinus tachycardia |
| | | |
| **Gastrointestinal disorders** | Nausea | Abdominal pain |
| | | Diarrhoea |
| | | Gastric irritation |
| | | Gastro-oesophageal reflux |
| | | Vomiting |
| | | |
| **Skin and subcutaneous tissue** | | Pruritus |

| | | |
|---|---|---|
| **disorders** | | |
| | | Rash |
| | | |
| **Renal and urinary disorders** | | Diuresis |
| | | Urinary retention* |

* Please refer to section 4.4 as theophylline may induce urinary retention in elderly males with pre-existing partial outflow obstruction.

## 4.9 Overdose

Over 3 g of Theophylline in an adult could result in serious toxicity (40mg/kg in a child). The fatal dose may be as little as 4.5 g in an adult (60mg/kg in a child), but is generally higher.

Symptoms

Warning: Serious features may develop as long as 12 hours after overdosage with prolonged release formulations.

Alimentary features: Nausea, vomiting (which is often severe), epigastric pain and haematemesis. Consider pancreatitis if abdominal pain persists.

Neurological features: Restlessness, hypertonia, exaggerated limb reflexes and convulsions. Coma may develop in very severe cases.

Cardiovascular features: Sinus tachycardia is common. Ectopic beats and supraventricular and ventricular tachycardia may follow.

Metabolic features: Hypokalaemia due to shift of potassium from plasma into cells is common, can develop rapidly and may be severe. Hperglycaemia, hypomagnesaemia and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

Management

Activated charcoal or gastic lavage should be considered if a significant overdose has been ingested within 1-2 hours. Repeated doses of activated charcoal given by mouth can enhance theophylline elimination. Measure the plasma potassium concentration urgently, repeat frequently and correct hypokalaemia. BEWARE! If large amounts of potassium have been given, serious hyperkalaemia may develop during recovery. If plasma potassium is low, then the plasma magnesium concentration should be measured as soon as possible.

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.

Measure the plasma theophylline concentration regularly when severe poisoning is suspected, until concentrations are falling. Vomiting should be treated with an antiemetic such as metoclopramide or ondansetron.

Tachycardia with an adequate cardiac output is best left untreated. Beta-blockers may be given in extreme cases but not if the patient is asthmatic. Control isolated convulsions with intravenous diazepam. Exlude hypokalaemia as a cause.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Xanthines

ACT code: R03D A04

Theophylline is a bronchodilator. In addition it affects the function of a number of cells involved in the inflammatory processes associated with asthma and chronic obstructive airways disease. Of most importance may be enhanced suppressor T-lymphocyte activity and reduction of eosinophil and neutrophil function. These actions may contribute to anti-inflammatory prophylactic activity in asthma and chronic obstructive airways disease.

## 5.2 Pharmacokinetic properties

At steady state, dosing with UNIPHYLLIN CONTINUS tablets produces minimal peak to trough variation and plasma theophylline levels are maintained within the therapeutic range of 10 - 20 μg/ml throughout the 12 hour dosing interval. An effective plasma concentration is considered to be 8-12 μg/ml, although plasma concentrations up to 20 μg/ml may be necessary to achieve efficacy in some cases. Do not exceed 20μg/ml.

Theophylline is distributed through all body compartments, approximately 60% is bound to plasma proteins. It is metabolised in the liver and excreted mainly by the kidneys as 1, 3 dimethyluric acid, 1 methyluric acid and 3 methylxanthine; approximately 10% is excreted unchanged by a first order process.

The predominant factors which alter theophylline clearance are: age, body weight, diet, smoking habits, other drugs and cardiorespiratory or hepatic disease.

## 5.3 Preclinical safety data

In studies in which mice, rats and rabbits were dosed during the period of organogenesis, theophylline produced teratogenic effects.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Hydroxyethylcellulose
Povidone
Cetostearyl alcohol
Macrogol 6000
Talc
Magnesium stearate

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

## 6.5 Nature and contents of container

Blister packs (aluminium foil sealed to 250 μm PVC with a PVdC coating of at least 40 gsm thickness) containing 8 or 56 tablets.

Polypropylene containers with polyethylene lids containing 250 or 1000 tablets.

Not all pack sizes may be marketed.

## 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

Mundipharma Pharmaceuticals Limited
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Arkle Road
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## 8 MARKETING AUTHORISATION NUMBER

PA 1688/011/002

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

Date of first authorisation: 8th March 1989

Date of last renewal: 3rd February 2008

## 10 DATE OF REVISION OF THE TEXT

November 2013