# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

UNIPHYLLIN Continus 400 mg Prolonged-Release Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains theophylline 400 mg as theophylline monohydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged release tablet.

White, capsule shaped tablet with 'UNIPHYLLIN' on one side and marked 'U400' and the Napp logo 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.

UNIPHYLLIN CONTINUS tablets are indicated for use in adults and children aged 6 years and above (and weighing no less than 22 kg).
Theophylline should not be used as first drug of choice in the treatment of asthma in children.

### 4.2 Posology and method of administration

Posology

Asthma
*Adults and the elderly*
The usual maintenance dose is 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.

*Paediatric population aged 6 years and above (equating to body weight of 22 kg)*
The usual paediatric 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.

Clearance is increased in children compared to values observed in adult subjects. The rapid clearance observed in children decreases towards adult values in late teens. Therefore, lower dosages (based on usual adult dose) may be required for adolescents.

UNIPHYLLIN CONTINUS tablets should not be used in children below 6 years of age (or less than 22 kg, respectively). Other dosage forms are available that are more suitable for children aged less than 6 years (or less than 22 kg).

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.

General considerations
Theophylline distributes poorly into body fat, therefore mg/kg doses should be calculated on the basis of lean (ideal) bodyweight.

At doses of 200 mg 12-hourly in adults it is not generally necessary to monitor plasma theophylline levels.

Plasma theophylline concentration should ideally be maintained between 5 and 12 micrograms/ml. A plasma level of 5 micrograms/ml probably represents the lower level of clinical effectiveness. Significant adverse reactions are usually seen at plasma theophylline levels greater than 20 micrograms/ml. Monitoring of plasma theophylline concentrations may be required when:

- Higher dosages are prescribed;
- Patients have co-morbidities resulting in impaired clearance;
- Theophylline is co-administered with medication that reduces theophylline clearance.

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

It may be appropriate to administer a larger evening or morning dose in some patients, in order to achieve optimum therapeutic effect when symptoms are most severe e.g. at the time of the 'morning dip' in lung function.

In patients whose night time or day time symptoms persist despite other therapy and who are not currently receiving theophylline, then the total daily requirement of UNIPHYLLIN CONTINUS tablets (as specified above) may be added to their treatment regimen as either a single evening or morning dose.

Method of administration
Oral
These tablets must be swallowed whole and not broken, crushed or chewed as doing so may lead to a rapid release of theophylline with the potential for toxicity.

Missed dose
If a patient forgets to take a dose but remembers within 4 hours of the time the dose was due to be taken, the tablets can be taken straight away. The next dose should be taken at the normal time. Beyond 4 hours the prescriber may need to consider alternative treatment until the next dose is due.

**4.3 Contraindications**

Hypersensitivity to the xanthine group of drugs or to any of the excipients listed in section 6.1.

Theophylline is contraindicated in children under 6 months of age.

**4.4 Special warnings and precautions for use**

The patient's response to therapy should be carefully monitored – worsening of asthma symptoms requires medical attention.

Due to potential decreased theophylline clearance, dose reduction and monitoring of serum theophylline concentrations may be required in elderly patients and patients with:

- cardiac disease
- hepatic disease
- exacerbations of lung disease
- hypothyroidism
- fever
- viral infections

Due to potential increased theophylline clearance, dose increase and monitoring of serum theophylline concentrations may be required in patients with hyperthyroidism and cystic fibrosis.

However, it should be considered that hyperthyroidism treatment (e.g. carbimazole) itself reduces theophylline clearance and a reduced theophylline dosage may therefore be required (see section 4.5). Theophylline may:

- act as a gastrointestinal tract irritant and increase gastric secretion, therefore caution should be exercised in patients with peptic ulcers;
- exacerbate cardiac arrhythmias and therefore caution should be exercised in patients with cardiac disorders;
- exacerbate frequency and duration of seizures and therefore caution should be exercised in patients with history of seizures and alternative treatment considered.

Theophylline should be used with caution in patients with severe hypertension, or chronic alcoholism.

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

Particular care is advised in patients suffering from severe asthma who require acute theophylline administration. It is recommended that serum theophylline concentrations are monitored in such situations.

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

Caution should be used in patients with porphyria.

Care should be taken in patients suffering from insomnia.

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

The following increase clearance of theophylline and it may therefore be necessary to increase dosage of theophylline to ensure a therapeutic effect: aminoglutethimide, carbamazepine, isoprenaline, phenytoin, rifampicin, ritonavir, sulphinpyrazone, barbiturates and hypericum perforatum (St. John's Wort).

Smoking and alcohol consumption can also increase clearance of theophylline.

The following reduce clearance of theophylline and a reduced dosage may therefore be necessary to avoid side-effects: aciclovir, allopurinol, carbimazole, cimetidine, clarithromycin, diltiazem, disulfiram, erythromycin, fluconazole, interferon, isoniazid, methotrexate, mexiletine, nizatidine, pentoxifylline, propafenone, propranolol, thiabendazole, verapamil and oral contraceptives (see sections 4.4 and 4.9).

Theophylline has been shown to interact with some quinolone antibiotics including ciprofloxacin and enoxacin which may result in elevated plasma theophylline levels.

The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose reduced 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). There are conflicting reports concerning the potentiation of theophylline by influenza vaccine and physicians should be aware that interaction may occur resulting in increased serum theophylline levels. A reduction of dosage may also be necessary in elderly patients. Thyroid disease or associated treatment may alter theophylline plasma levels.

Concurrent administration of theophylline may:

- inhibit the effect of adenosine receptor agonists (adenosine, regadenoson, dipyridamol);
- oppose the sedatory effect of benzodiazepines;
- result in the occurrence of arrhythmias with halothane;
- result in thrombocytopenia with lomustine;
- increase urinary lithium clearance.

Theophylline may decrease steady state phenytoin levels.

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.

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.

Co-administration with ketamine may cause reduced convulsive threshold; with doxapram may cause increased CNS stimulation.

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

**4.6 Fertility, pregnancy and lactation**

Pregnancy
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.

Breastfeeding
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**

UNIPHYLLIN CONTINUS tablets have no or negligible influence on the ability to drive and use machines.

**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 |
| | | Sleep disorder |
| | | |
| **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 disorders** | | Pruritus |
| | | 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 urinary tract obstruction.

Reporting of 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: +3553 1 6764971; Fax: + 353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

**4.9 Overdose**

Theophylline has a low therapeutic index. Theophylline toxicity is most likely to occur when serum concentrations exceed 20 micrograms/ml and becomes progressively more severe at higher serum concentrations.

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

**Symptoms**

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

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

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

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

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

Management

Activated charcoal or gastric 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. Exclude hypokalaemia as a cause.

Particularly in the setting of theophylline overdose induced convulsions, efficacy of some anticonvulsant drugs, such as benzodiazepines, may be reduced through suspected pharmacodynamic interactions.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, xanthines

ATC 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.

Theophylline stimulates the myocardium and produces a diminution of venous pressure in congestive heart failure leading to marked increase in cardiac output.

### 5.2 Pharmacokinetic properties

Absorption

Following oral administration, theophylline is efficiently absorbed and is associated with an absolute bioavailability approximating 100%. Following oral administration of UNIPHYLLIN CONTINUS tablets, the delivery of theophylline is controlled and, at steady state, peak concentrations are typically seen after approximately 5 hours.

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 micrograms/ml throughout the 12 hour dosing

interval. An effective plasma concentration is considered to be 8-12 micrograms/ml, although plasma concentrations up to 20 micrograms/ml may be necessary to achieve efficacy in some cases. Do not exceed 20 micrograms/ml.

Distribution and protein binding
Theophylline is distributed through all body compartments, approximately 60% is bound to plasma proteins.

Biotransformation and elimination
Theophylline 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 mean elimination half life associated with UNIPHYLLIN CONTINUS tablets is approximately 7 hours.

Factors affecting clearance
The predominant factors which alter theophylline clearance are: age, body weight, diet, smoking habits, other drugs and cardiorespiratory or hepatic disease. Clearance is increased in children compared to values observed in adult subjects. Clearance decreases towards adult values in late teens.

Linearity
Studies involving prolonged-release UNIPHYLLIN CONTINUS tablets have demonstrated approximately dose-proportional pharmacokinetics across the 200-600 mg dose range.

**5.3 Preclinical safety data**

Genotoxicity and carcinogenicity
Both positive and negative results have been reported in in-vitro and in-vivo assays of genotoxicity with theophylline. However, oral theophylline administered daily to rats and mice for 2 years did not show carcinogenicity. Therefore, it is unlikely that theophylline poses a carcinogenic risk in humans.

Reproductive and developmental toxicity
Theophylline has been shown to have adverse effects upon the male reproductive system in rodents.

Embryofetal development studies in rats and mice have demonstrated fetotoxicity, independent from maternal toxicity. An embryofetal development study in rabbits reported teratogenic effects in conjunction with maternal toxicity. Therefore, theophylline should be considered to have the potential for fetotoxicity and embryofetal developmental toxicity in humans.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Hydroxyethylcellulose
Povidone (K25)
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**

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**8 MARKETING AUTHORISATION NUMBER**

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Date of last renewal: 3rd February 2008

**10 DATE OF REVISION OF THE TEXT**

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