SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

UNIPHYLLIN 200mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 200 mg theophylline as 220 mg theophylline monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet

White, capsule shaped tablet, plain on one side and marked ‘U200’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment and prophylaxis of bronchospasm associated with asthma, chronic obstructive pulmonary disease and chronic bronchitis. Also indicated for the treatment of left ventricular and congestive cardiac failure.

UNIPHYLLIN tablets are indicated for use in adults and children aged 6 years and above.

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

Adults and the elderly
The usual maintenance dose is 200 mg 12 hourly. This may be titrated to either 300 mg or 400 mg dependent on the therapeutic response.

Paediatric population aged 6 years and above
The usual paediatric maintenance dose is 9 mg/kg twice daily. Some children with chronic asthma require and tolerate much higher doses (10-16 mg/kg twice daily).

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 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.

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

Plasma theophylline concentrations 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 the dose on an individual basis.

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 tablets (as specified above) may be added to their treatment regimen as either a single evening or morning dose.

Dose adjustment may be necessary if smoking started or stopped during treatment.

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 theophylline and other xanthines or to any of the excipients listed in section 6.1.
Patients with porphyria.
Concomitant administration with ephedrine in children less than 6 years of age (or less than 22 kg).
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 arrhythmias or other 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 when starting acute hyperthyroidism treatment) and cystic fibrosis.

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.

Use 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.

4.5 Interaction with other medicinal products and other forms of interaction

The following medicinal products may increase theophylline plasma concentrations: cimetidine, ciprofloxacin, macrolide antibiotics such as erythromycin, propranolol, isoniazid, oral contraceptives, mexiletine, ranitidine, fluvoxamine.

The following increase clearance of theophylline and it may therefore be necessary to increase dosage 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 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, valaciclovir, verapamil and oral contraceptives (see section 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) and may reduce their toxicity when used for cardiac perfusion scanning;
- oppose the sedatory effect of benzodiazepines;
- result in the occurrence of arrhythmias with halothane;
- result in thrombocytopenia with lomustine;
- increase urinary lithium clearance.

Therefore these drugs should be used with caution.

Theophylline may decrease steady state phenytoin levels.

Hypokalaemia resulting from $beta_2$ 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 potassium concentrations are monitored in such situations.

Care should be taken in its concomitant use with β-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 clearly necessary.

Breastfeeding

Theophylline is secreted in breast milk, and may be associated with irritability in the infant, therefore it should only be given to breastfeeding women when the anticipated benefits outweigh the risk to the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following adverse drug reactions have been reported in the post-marketing setting for theophylline. Frequencies of "not known" have been assigned as accurate frequencies cannot be estimated from the available clinical trial data.

Immune system disorders	Anaphylactic reaction
	Anaphylactoid reaction
	Hypersensitivity
Metabolism and nutrition disorders	Hyperuricaemia
Psychiatric disorders	Agitation
	Anxiety
	Insomnia
	Sleep disorder
Nervous system disorders	Convulsions
	Dizziness
	Headache
	Tremor

Cardiac disorders	Atrial tachycardia
	Palpitations
	Sinus tachycardia
	Arrhythmias
Gastrointestinal disorders	Abdominal pain
	Diarrhoea
	Gastric irritation
	Gastro-oesophageal reflux
	Nausea
	Vomiting
	Gastrointestinal discomfort
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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

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 could be serious in an adult (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: Agitation, restlessness, hypertonia, exaggerated limb reflexes, convulsions, seizures, mydriasis. 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 an 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 tablets, the delivery of theophylline is controlled and, at steady state, peak concentrations are typically seen after approximately 5 hours.

An effective plasma concentration is considered to be 5-12 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.

An effective plasma concentration is considered to be 5-12 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.

Biotransformation

Theophylline is metabolised in the liver to 1, 3-dimethyl uric acid and 3-methylxanthine.

Elimination

Theophylline and its metabolites are excreted mainly in the urine. Approximately 10% is excreted unchanged. The mean elimination half-life associated with UNIPHYLLIN 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 tablets have demonstrated approximately dose-proportional pharmacokinetics across the 200-600 mg dose range.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Genotoxicity and carcinogenicity

In vitro and *in vivo* assays have shown both positive and negative genotoxic results for 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 effects upon the male reproductive system in rodents, but at doses considered in excess of the maximum human dose indicating little relevance to clinical use.

Several embryofetal development studies in rats, mice and rabbits have demonstrated developmental effects independent from maternal toxicity at high doses of theophylline. Therefore, theophylline should be considered to have the potential for 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

Three years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

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

Polypropylene containers containing 60, 100, 250 or 1000 tablets.

Amber glass bottles containing 50 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd
Unit G4, Riverside Industrial Estate,
Riverside Way,
Dartford, DA1 5BS, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0063

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 August 1979 / 15 May 2003

10 DATE OF REVISION OF THE TEXT

15/08/2025