SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Unicontin 400 (Controlled Release Tablets of Theophylline 400 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each controlled release tablet contains:
Theophylline BP/Ph.Eur. 400.00 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Controlled release tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of symptoms and prophylaxis of reversible bronchospasm associated with asthma and chronic obstructive pulmonary disease.

4.2 Posology and Method of Administration

Unicontin 400 mg tablets may be taken once a day in the morning or evening. It is recommended that Unicontin be taken with meals. Patients should be advised that if they choose to take Unicontin with food it should be taken consistently with food and if taken in a fasted condition it should routinely be taken fasted. The product whenever dosed should be dosed consistently with or without food.

Unicontin tablets must be swallowed and not chewed. Safety and effectiveness in children under 12 years of age have not been established with Unicontin tablets.

A. Dosing Initiation and Titration – Patients without risk factors for impaired clearance:

Titration Step	Children <45 kg (12–15 years)	Children >45 kg (16–60 years)
1 – Starting dose	12–14 mg/kg/day up to max 300 mg/day OD	300–400 mg/day OD
2 – After 3 days, if tolerated	16 mg/kg/day up to max 400 mg/day OD	400–600 mg/day OD
3 – After 3 more days, if tolerated and needed	20 mg/kg/day up to max 600 mg/day OD	As with all products, doses >600 mg should be titrated according to blood level

B. Patients with risk factors for impaired clearance, the elderly (>60 years), and those in whom it is not feasible to monitor serum theophylline concentrations:

In children 12–15 years of age, the theophylline dose should not exceed 16 mg/kg/day up to a maximum of 400 mg daily in the presence of risk factors for reduced theophylline clearance or if it is not feasible to monitor serum theophylline concentrations. In adolescents >16 years and adults, including the elderly, the theophylline dose should not exceed 400 mg/day in the presence of risk factors for reduced theophylline clearance or if it is not feasible to monitor serum theophylline concentrations.

Dosage Adjustment Based upon Serum Theophylline Concentration:

Peak Serum Concentration	Dosage Adjustment
<9.9 mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 days.
10–14.9 mcg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6–12 month intervals. If symptoms are not controlled and current dosage is tolerated, consider adding additional medication(s).
15–19.9 mcg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated.
20–24.9 mcg/mL	Decrease dose by 25% even if no adverse effects are present. Recheck serum concentration after 3 days.

25–30 mcg/mL	Skip next dose and decrease subsequent doses by at least 25% even if no adverse effects are present. Recheck serum concentration after 3 days. If symptomatic, consider whether overdose treatment is indicated.
>30 mcg/mL	Treat overdose as indicated. If theophylline is subsequently resumed, decrease dose by at least 50% and recheck serum concentration after 3 days.

*Dose reduction and/or serum theophylline concentration measurement is indicated whenever adverse effects are present, physiologic abnormalities that can reduce theophylline clearance occur or a drug that interacts with theophylline is added or discontinued.

Maintenance Therapy: Careful clinical titration is important to assure patient acceptance and safety of the medication. Patients, when stabilised as established by serum theophylline concentration or respiratory function, usually remain controlled without further dosage adjustment. Serum theophylline levels should be measured periodically (at 6 to 12 month intervals) even in clinically controlled patients. The elderly as well as patients with congestive heart failure, cor pulmonale and/or liver disease may have unusually low dosage requirements and thus may experience toxicity even at the recommended dosage.

4.3 Contraindications

Patients with a history of hypersensitivity to theophylline or other components in the product; porphyria; concomitant administration with ephedrine in children.

4.4 Special Warnings and Precautions for Use

Serum levels above 20 mcg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses may result in increased serum levels and potential toxicity.

Reduced theophylline clearance has been documented in the following groups:

(1) patients with impaired liver function;

(2) patients over 60 years of age, particularly males and those with chronic lung disease;

(3) those with cardiac failure from any cause;

(4) patients with acute febrile illness;

(5) neonates and infants;

(6) hypothyroidism;

(7) shock;

(8) sepsis with multi-organ failure; and

(9) those patients taking certain drugs.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Whenever a patient receiving theophylline develops nausea and vomiting, particularly repetitive vomiting, or other signs and symptoms consistent with theophylline toxicity (even if another cause may be suspected), additional doses of theophylline should be withheld and a serum theophylline concentration measured immediately.

Use with caution in patients with cardiac arrhythmias, peptic ulcer, hyperthyroidism, severe hypertension and chronic alcoholism. Avoid concomitant use with other xanthine-containing products. The hypokalaemia resulting from beta agonist therapy, steroids, diuretics and hypoxia may be potentiated by xanthines. It is recommended that serum potassium levels are monitored in severe asthmatics who require hospitalisation. Alternative treatment is advised for patients with a history of seizure activity.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Agents that decrease theophylline plasma levels:

Agent	**Agent**
Rifampicin	Barbiturates
Charcoal	Hydantoins[1]
Ketoconazole	Thioamines[2]
Smoking (Cigarettes and Marijuana)	Sulfinpyrazone
Sympathomimetics (β-agonists)	Carbamazepine[3]

Isoniazid[3]	Loop Diuretics[3]
Isoprenaline	Alcohol

Agents that increase theophylline plasma levels:

Agent	**Agent**
Allopurinol	Corticosteroids
Beta blockers (non-selective)	Disulfiram
Calcium channel blockers	Ephedrine
Cimetidine	Influenza virus vaccine
Oral Contraceptives	Interferon
Mexiletine	Macrolides
Thiabendazole	Quinolones
Carbamazepine[3]	Thyroid hormones[4]
Loop diuretics[3]	Isoniazid[3]
Fluconazole	Fluvoxamine
Nizatidine	Methotrexate
Propafenone	Oxpentifylline
Ticlopidine	Tacrine

[1] Decreased hydantoin levels may also occur. [2] Increased theophylline clearance in hyperthyroid patients. [3] May increase or decrease theophylline levels. [4] Decreased theophylline clearance in hypothyroid patients.

The sedative effects of benzodiazepines may be antagonised by theophylline. Beta-agonists and theophylline act synergistically in vitro; an additive effect has also been demonstrated in vivo. Halothane with theophylline has resulted in catecholamine-induced arrhythmias. Theophylline decreases plasma levels of zafirlukast. Ketamine and theophylline co-administration has resulted in extensor-type seizures. Lithium plasma levels may be reduced by theophylline. A dose-dependent reversal of neuromuscular blockade by theophylline may occur with non-depolarising muscle

relaxants. Probenecid may increase the pharmacologic effects of theophylline due to decreased theophylline renal excretion. Theophyllines may antagonise the sedative effects of propofol.

The herbal remedy Hypericum perforatum should not be taken concomitantly with Unicontin tablets.

Drug/Food Interactions: The absorption characteristics of Unicontin tablets (theophylline anhydrous) are enhanced by co-administration with food.

4.6 Fertility, Pregnancy and Lactation

Category C – There are no adequate and well controlled studies in pregnant women and there are no teratogenicity studies in non-rodents. Embryotoxicity was observed in rats at a dose of 220 mg/kg in the absence of maternal toxicity. Theophylline should not be administered during pregnancy unless considered essential by the physician.

Theophylline is secreted in breast milk and may cause irritability or other signs of toxicity in nursing infants. A decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Children: Safety and efficacy in children below 12 years of age has not been established.

4.7 Effects on Ability to Drive and Use Machines

No known effects.

4.8 Undesirable Effects

Side effects are usually associated with the serum concentration of theophylline.

Serum Theophylline Concentration	Adverse Reaction
< 20 mcg/mL	Nausea, vomiting, headache, insomnia, tachypnoea, epigastric pain, palpitation, hypotension, irritability.
> 20 mcg/mL	Persistent vomiting, cardiac arrhythmias, intractable seizures, tachycardia.

Others: alopecia, hyperglycaemia, inappropriate ADH syndrome, rash.

In a small percentage of patients the caffeine-like adverse effects persist during maintenance therapy even at peak serum theophylline concentration within the therapeutic range (10–20 mcg/mL). Dosage reduction may alleviate the adverse effects in these patients.

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.

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdose Symptoms: Overdose with theophylline may be manifested by symptoms such as vomiting, abdominal pain, acid/base disturbance, rhabdomyolysis, sinus tachycardia, ventricular arrhythmias, nervousness and seizures.

Treatment of Overdosage: Empty stomach contents. Monitor electrocardiogram and maintain fluid balance. Oral activated charcoal has been found to reduce high theophylline serum concentrations. In severe poisoning, employ charcoal column haemoperfusion. Treat symptoms on appearance. The physician should be aware that tablets in the intestine will continue to release theophylline for a period of hours. In the event of hypokalaemia, potassium chloride should be given by slow intravenous infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Theophylline has two distinct actions: smooth muscle relaxation (e.g. bronchodilation) and suppression of the response of the airways to stimuli (i.e. non-bronchodilator prophylactic effects). Bronchodilation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III and to a lesser extent, PDE IV) while non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanisms. Theophylline increases the force of contraction of diaphragmatic muscles through enhancement of calcium uptake through an adenosine-mediated channel.

Serum Concentration-Effect Relationship: Theophylline has a particularly well-defined therapeutic range with concentrations from 5–20 mcg/ml giving an optimum compromise between efficacy and toxicity. At serum theophylline concentrations >20 mcg/mL, both the frequency and severity of adverse reactions increase.

5.2 Pharmacokinetic Properties

Unicontin tablets are of the same composition and manufactured by the same process as Uniphyl tablets (registered trademark of Purdue Pharmaceuticals Products L.P.). The bioavailability of theophylline from two 400 mg tablets has been found to be twice that from a single 400 mg tablet, consistent with dose proportionality. The bioavailability of theophylline relative to immediate-release aminophylline tablets increased from 53 ± 23% to 96 ± 46% when taken under extreme fasting and non-fasting (high fat content meal) conditions, respectively, without evidence of dose dumping.

In 12 patients with reversible chronic obstructive pulmonary disease given once-daily dosage of two 400 mg Unicontin tablets for seven days, mean Cmax was 15.1 mcg/ml; tmax 7.6 hours; and trough theophylline levels 8.6 and 7.9 mcg/ml just before the final dose and 24 hours later, respectively. This demonstrates that once-daily dosing maintains theophylline serum levels within the therapeutic range over 24 hours.

Evening dosing of Unicontin 400 mg tablets is particularly useful for controlling nocturnal episodes of asthma attacks.

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

Povidone K-30 (Kollidon 30), Hydroxyethyl Cellulose (Natrosol 250 HX), Cetostearyl Alcohol (Kolliwax CSA 50), Purified Talc, Magnesium Stearate, Purified Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years (36 months).

6.4 Special Precautions for Storage

Store at or below 25°C in a dry place, protected from light. Keep out of reach of children.

6.5 Nature and Contents of Container

Primary Packaging Material: Unicontin tablets 400 mg are packed in blister strips comprising of PVDC coated PVC film (104 mm/0.25 mm) backed with aluminium foil (0.025 mm).

Secondary Packaging Material: The blister strip of 10s is packaged in an outer carton with a package insert.

Pack Sizes: Box of 100 tablets (10×10s blister strips); Box of 30 tablets (3×10s blister strips).

6.6 Special Precautions for Disposal and Other Handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Modi-Mundipharma Pvt. Ltd.

1400, Modi Tower, 98, Nehru Place, New Delhi – 110019, India.

8. MARKETING AUTHORISATION NUMBER(S)

H2009/18923/121

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

14 April 2009.

10. DATE OF REVISION OF THE TEXT

14 March 2023.