SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of medicinal product

Unicontin 400
(Controlled Release Tablets of Theophylline)

2. Qualitative and Quantitative composition

Ingredient	Reference standard	Quantity mg / tablet	Function
Theophylline	BP/Ph.Eur.	400.00	Active
Povidone K - 30 (Kollidon 30)	USP	3.00	Binding agent
Hydroxyethyl Cellulose (Natrosol 250 HX)	BP/Ph.Eur.	10.00	Stabilizing agent
Kolliwax CSA 50 (Cetostearyl Alcohol)	BP/Ph.Eur.	33.67	Binding agent
Purified Talc	BP/Ph.Eur.	10.00	Lubricant
Magnesium Stearate	BP/Ph.Eur.	10.00	Lubricant
Purified water	BP/Ph.Eur.	0.22 ml*	Solvent

*Not present in the final weight

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 they take it in a fasted condition, it should routinely be taken fasted. It is important that the product whenever dosed be dosed consistently with or without food.

Unicontin tablets must be swallowed and not chewed. Infrequently, patients receiving Unicontin tablets may pass an intact matrix tablet in the stool or via colostomy. These matrix tablets usually contain little or no residual theophylline.

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

Dosing initiation and Titration (as anhydrous theophylline)

A. Patients without risk factors for impaired clearance.

Titration sleep		**Children < 45kg (12-15 years)**	**Children > 45kg (16-60 years)**
1	Starting dosage	12-14mg/kg/day up to maximum of 300mg/day administered OD	300mg-400mg /day administered OD
2	After 3 days, if tolerated, increased dose to :	16mg/kg/day up to a maximum 400mg/day administered OD	400mg-600mg /day administered OD
3	After 3 more days, if tolerated and if needed increased dose to :	20mg/kg/day up to a maximum 600mg/day administered OD	As with all product doses > 600mg 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 16mg/kg/day up to a maximum of 400mg 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
<9.9mcg/mL	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after three days for further dosage adjustment.
10-14.9mcg/mL	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6-12 months intervals. * If symptoms are not controlled and current dosage is tolerated, consider adding additional medication (s) to treatment regimen.
15-19.9mcg/mL	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated. *
20-24.9mcg/mL	Decrease dose by 25% even if no adverse effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment.
25-30mcg/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 to guide further dosage adjustment. If symptomatic, consider whether overdose treatment is indicated.
>30mcg/mL	Total overdose as indicated. If theophylline is subsequently resumed, decrease dose by at least 50% and recheck, serum concentration after 3 days to guide further dosage adjustment.

*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. It should be borne in mind however that for reasons stated in the warnings & precautions section, dosage adjustments may be necessary. 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, corpulmonale and/or liver disease may have unusually low dosage requirements and thus may experience toxicity even at the recommended dosage.

Do not maintain any dose that is not tolerated.

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 Warnings and Precautions

Serum levels above 20mcg/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 readily identifiable 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. Toxic accumulation may occur in above cases. Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug. Reduction of dosage and laboratory monitoring are especially appropriate in the above individuals. Severs side effects (cramps, convulsions, supraventricular tachycardia) may appear at very high serum concentrations. Patients once titrated to an effective dose, should not be changed from theophylline tablets preparations to other slow or sustained release xanthine preparations without re-titration and clinical assessment.

Serious side effects such as ventricular arrhythmias, convulsions or event 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 with held and a serum theophylline concentration measured immediately. Patients should be instructed not to continue any dosage that causes adverse effects and to withhold subsequent doses until the symptoms have resolved, at which time the clinician may instruct the patient to resume the drug at a lower dosage.

Careful consideration of the various interacting drug and physiologic conditions that can alter theophylline clearance and require dosage adjustment should occur prior to initiation of theophylline therapy, prior to increase in theophylline dose, and during follow up. The dose of theophylline selected for initiation of therapy should be low and, if tolerated, increased slowly over a period of a week or longer with the final dose guided by monitoring serum theophylline concentrations and the patient's clinical response.

On an average, theophylline half-life is shorter in cigarette and marijuana smokers than in non-smokers, but smokers can the have theophylline half-lives as along as non-smokers.

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. Particular care is advised in patients suffering form severe asthma who require hospitalization. It is recommended that serum potassium levels are monitored in such situation. Alternative treatment is advised for patients with a history of seizure activity.

4.5 Interaction with other medicinal products and other forms of interactions:

The following drugs interactions have been demonstrated with theophylline:

Agents that decrease theophylline plasma levels

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:

Allopurinol	Corticosteroids
Beta blockers (nonselective)	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 clearances in hyperthyroid patients
[3] May increase or decrease theophylline levels.
[4] Decreased theophylline clearances in hypothyroid patients.

The sedative effects of benzodiazepines may be antagonized by theophylline, although their pharmacokinetics do not appear to be altered. Co-administration may be beneficial in reversing sedation produced by benzodiazepines.

Beta-agonists and theophylline act synergistically in vitro; and additive effect has also been demonstrated in vivo.
Halothane with theophylline has resulted in catecholamine-induced arrhythmias.
Theophylline decreases plasma level of zafirlukast.
Ketamine and theophylline co-administration has resulted in extensortype seizures.
Lithium plasma levels may be reduced by theophylline.
A dose-dependent reversal of neuromuscular blockade by theophylline may occur with nondepolarizing muscle relaxants.
Probenecid may increase the pharmacologic effects of theophylline due to decreased theophylline renal excretion.
Theophyllines may antagonize the sedative effects of propofol.
Case reports suggest that theophylline plasma levels may be increased by ranitidine, possibly increasing pharmacologic and toxic effects. However, several controlled studies indicate that an interaction does not occur. It appears that if this interaction occurs, it is rare.
The incidence of theophylline adverse reaction may possibly be enhanced by concurrent use of tetracyclines.
The herbal remedy Hypericum perforatum should not be taken concomitantly with Unicontin tablets. If the patient is already taking Hypericum perforatum, the doctor should be consulted before stopping the preparations.

Drug/Food interactions:

The absorption characteristics of Unicontin Continus tablets (theophylline anhydrous) have been studied and are enhanced by co-administration with food.

4.6 Pregnancy and lactation

Category C-There is 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 220mg/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. Because of the potential for serious adverse reactions in nursing infants from theophylline, 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
< 20mcg/mL	Nausea, vomiting, headache, insomnia, tachypnea, epigastric pain, palpitation, hypotension, irritability.
> 20mcg/mL	Persistent vomiting, cardiac arrhythmias, intractable seizures, tachycardia.

Others: alopecia, hyperglycemia, 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 (10-20mcg/mL). Dosage reduction may alleviate the adverse effects in these patients. However, persistent adverse effects should result in revaluation of the need for continued theophylline therapy and the potential therapeutic benefit of alternative treatment.

4.9 Overdose & Its Treatment

Overdose

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 hypokalemia, potassium chloride should be given by slow intravenous infusion. Repeated measurement of plasma potassium should be made.

5.0 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). Studies suggest that 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, that do not involve inhibition of PDE III or antagonism of adenosine receptors. Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

Serum Concentration-Effect Relationship: Theophylline is often thought of as a drug which has a particularly well-defined therapeutic range with concentration from 5-20mcg/ml giving an optimum compromise between efficacy and toxicity. At serum theophylline concentration >20mcg/mL, both the frequency and severity of adverse reaction increase.

5.2 Pharmacokinetic properties

Uniphyl tablets are registered trademark of the Purdue Pharmaceuticals Products L.P. and are marketed in the USA. Unicontin tablets are of the same composition and manufactured by the same process as that of the Uniphyl tablets. Thus, the Clinical Trial studies carried out on Uniphyl tablets are also valid for Unicontin tablets.

The bioavailability of theophylline from two 400mg tablets has been found to be twice that from a single 400mg tablet, as expected for dose proportionality. The 12 healthy male subjects in the study showed a mean. area under serum theophylline curve (AUC) and peak level of theophylline (C_{max}) twice as great with the 800mg dose as with the 400mg dose. The times of attainment of the peak level of theophylline (t_{max}) were the same for the two doses.

Recently, the effect of food was investigated in a l2-subject (healthy male non-smokers) three-way comparative, single-dose, randomized, crossover study. The bioavailability of theophylline relative to immediate- release Aminophylline tablets increased from 53 ± 23 % to 96 ± 46 % when Uniphyl (two tablets of 400mg) was taken under extreme fasting and non fasting (high fat content meal l conditions, respectively. Despite the increase in absorption of theophylline from the Uniphyl tablets there was no evidence of "dose dumping".

A group of 12 patients with reversible chronic obstructive pulmonary disease (COPO) were given the same once-daily dosage regimen as were the healthy subjects of the crossover morning doses of study described above, i.e. single two 400mg Uniphyl tablets for seven days. The following mean values were

computed from the data: C_{max}, 15.1 mcg/ml; t_{max}, 7.6 hours; trough theophylline levels, 8.6 and 7.9 mcg/ml just before the final dose and 24 hours later , respectively. This demonstrates that with single once-daily dosing of Uniphyl tablets theophylline serum levels remained within the therapeutic values over 24 hours.

To determine the bioavailability properties of Uniphyl tablets administered once in 24 hours in comparison with the twice-daily administered Theo-Dur tablets, 20 patients with stable asthma were studied under steady-state conditions for the pharmacokinetic relationships between the two dose regimens. The 24-hour serum theophylline profiles were similar, with a double peak for Theo- Dur and a broad single peak for Uniphyl.

As the once-daily dosing of Uniphyl 400mg tablets in the evening hours is claimed to be especially useful for controlling nocturnal episodes of asthma attacks, a number of bioavailability studies were performed in asthmatic patients to whom Uniphyl 400mg tablets were administered once daily in the evening. Nine stable asthmatics receiving a theophylline preparation two or more times daily were transferred to Uniphyl tablets, 2 x 400mg given at 8 p.m. The average maximum theophylline concentration, reached at 7.6 hours, was 13.7 mcg / ml whereas the minimum was 6.2 mcg / ml. None of the patients in either study had exacerbation of symptoms or side effects. No evidence of "dose dumping" related to postprandial use of Uniphyl tablets was seen.

5.3 Preclinical Safety Data

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

6.0 Pharmaceutical Particulars

6.1 List of Excipients

1. Povidone K – 30 (Kollidon 30)
2. Hydroxyethyl Cellulose (Natrosol 250 HX)
3. Cetostearyl Alcohol (Dehydag Wax O / Lanette O)
4. Purified Talc
5. Magnesium Stearate
6. 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 30ºC, in a dry place, protected from light.

6.5 Nature and content of container

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

Box of 100 tablets (10×10's blister strips)

6.6 Instructions for use/handling

No special requirements.

7.0 Name and address of marketing authorization holder

Registered by: -

Modi-Mundipharma Pvt. Ltd.
1400, Modi Tower,
98, Nehru Place,
New Delhi – 110019, India.
Phone: +91-11-42504555
Fax: +91-11-26451659
E-mail: mithu.sen@winmedicare.com

8.0 Marketing authorization number

Fresh Registration

9.0 Date of first authorization/renewal of the authorization

Fresh Registration

10.0 Date of (partial) revision of the text

January 2023