UFT Capsules (uracil-tegafur)

PROPRIETARY NAME
(and dosage form):

UFT Capsules

COMPOSITION
Each capsule contains 100 mg **tegafur**, a prodrug of 5-fluorouracil and 224 mg **uracil**.

PHARMACOLOGICAL CLASSIFICATION
A26 Cytostatic agents

PHARMACOLOGICAL ACTION
Mechanism of Action
UFT is an anticancer medication composed of a fixed molar ratio (1:4) of tegafur and uracil to be administered with calcium folinate. In the body, tegafur is converted into 5-fluorouracil (5-FU), the active antineoplastic metabolite. The mechanism of cytotoxicity of 5-FU is thought to be derived from the fact that 5-fluoro-deoxyuridine-monophosphate (FdUMP), the active metabolite of 5-FU, competes with deoxyuridine-monophosphate (dUMP), thereby inhibiting thymidylate synthase and subsequently DNA synthesis. Another active metabolite of 5-FU, 5-fluorouridine-triphosphate (FUTP) is integrated into cellular RNA, inhibiting RNA function. Uracil, when combined with tegafur, enhances the antitumor activity of 5-FU due to higher 5-FU concentrations in the tumor tissue versus normal surrounding tissue compared with tegafur alone.
Calcium folinate enhances the cytotoxicity of 5-FU. The independent actions of uracil and leucovorin calcium provide for dual biomodulation of tegafur.
Pharmacokinetics
After a single dose of tegafur (100 to 400 mg)/ uracil (224 to 896 mg), plasma tegafur increased proportional to dose. Uracil and 5-FU C_{max} values increased proportionally, whereas AUC's increases on 400 mg were about 6 fold higher than with 100 mg. Single dose calcium folinate (25 mg) resulted in maximal plasma concentrations of d,l-leucovorin calcium and 5-methyl tetrahydrofolate of 402 ng/mL and 345 ng/mL, respectively.
Following UFT 300 mg/m^2/day, in three divided doses, tegafur plasma concentrations of >1000 ng/mL are maintained throughout each 8 hour dosing interval, whereas uracil concentrations decline rapidly following C_{max}. 5-FU plasma concentrations peak 30 to 60 minutes after administration, at approximately 200 ng/mL, and remain detectable for each 8-hour dosing interval. No significant accumulation of tegafur, uracil or 5-FU occurs over a 28-day course.
Absorption
Tegafur, uracil and leucovorin calcium are rapidly absorbed into the systemic circulation, peak plasma concentrations being achieved within 1 to 2 hours. Concurrent administration of oral leucovorin calcium does not significantly alter the plasma pharmacokinetics of tegafur, uracil or 5-FU. Similarly, UFT does not affect the oral absorption of calcium folinate.
Distribution
Serum protein binding of tegafur is 52%. Serum protein binding of uracil is negligible.
Metabolism
Conversion of tegafur to 5-FU occurs via C-5'oxidation and C-2'hydrolysis. Microsomal oxidation of tegafur is mediated to some extent by human cytochrome P_{450} 2A6.
Excretion
Less that 20% of administered tegafur is excreted intact in the urine following oral administration. The terminal elimination t½ of tegafur is 11 hours and that of uracil is 20 to 40 minutes.
Special Population: Kinetics in patients with impaired renal and hepatic function has not been studied.

INDICATIONS
UFT is indicated for the first-line treatment of metastatic colorectal cancer with calcium folinate.

CONTRA-INDICATIONS
Patients who have experienced hypersensitivity to tegafur, uracil, 5-fluorouracil (5-FU) or any component of the formulation.
Pregnancy and lactation.
The safety and efficacy of UFT in patients in paediatrics, children and adolescents has not been established.

WARNINGS

Hepatic Disorders

Hepatic disorders including fatal fulminante hepatitis have been reported and therefore patients receiving UFT/calcium folinate who present with signs and symptoms of hepatitis or other liver disease should have clinical and laboratory tests performed as appropriate.

Diarrhoea

UFT/calcium folinate can induce diarrhoea. If Common Toxicity Criteria (CTC) grade 2 or greater diarrhoea occurs, interruption of medication should be considered, with supportive care initiated as indicated. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement to prevent potential dehydration.

Pregnancy

UFT can cause foetal harm when administered to pregnant women. There is no specific experience with UFT in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while taking UFT. If UFT is used during pregnancy, or if the patient becomes pregnant while taking it, she should be advised of the potential harm to the foetus.

DOSAGE AND DIRECTIONS FOR USE

Metastatic Colorectal Cancer

The usual dose is 300 mg/m^2/day tegafur plus 90 mg/day calcium folinate (30 mg/dose) administered in three divided doses (every 8 hours) orally one hour before or one hour after meals for 28 consecutive days. If the total number of UFT capsules cannot be evenly divided, the highest dose should be given in the morning and lower doses in the afternoon or evening. Courses may be repeated every 35 days. If doses are missed or the medication is interrupted by the physician, missed doses are not made up during the course. Treatment is not usually extended beyond day 28 within a course. Calcium folinate tablets should be taken at the same time as UFT capsules. Table 1 represents the total daily dose by body surface area (BSA) and the number of capsules/tablets to be taken per day.

TABLE 1
Total Daily Dose by Body Surface Area

Body Surface Area (m^2)	No. of UFT (100 mg) capsules per day	No. of Calcium Folinate (15 mg) tablets per day
<1.17	3	6
1.17-1.49	4	6
1.50-1.83	5	6
>1.83	6	6

Dose Modification Guideline

Toxicity may be managed using UFT dose modification scheme described in Table 2. Calcium folinate dose remains unchanged. If the UFT treatment is interrupted, calcium folinate treatment should also be interrupted.

TABLE 2
UFT Dose Modification Scheme

Non-Haematologic Toxicity	Worst CTC* Grade Toxicity	UFT Dose Reduction[a] in mg/m^2/day
	0-1	No change
	2[b]	No change
	3-4[b]	50[b]
Haematologic Toxicity	0-2[c]	No change
	3-4[c]	50[c]

* CTC –Common Toxicity Criteria

a) UFT dose reductions expressed as a decrease in mg/m^2/day of the preceding dose, based on the worst grade of non-haematologic or haematologic toxicity (granulocyte count or platelet count only). The minimum dose reduction is 1 UFT capsule per day.

b) Therapy withheld until toxicity resolves to $\leq$ baseline or $\leq$ grade 1.

c) Therapy withheld until granulocytes $\geq$ 1500/mm^3 and platelets $\geq$ 100,000/mm^3.
For level 3-4 toxicity, dose reduction maintained for remainder of cycle.

In the event that because of rounding of doses, a patient who receives a dose reduction according to Table 2, would receive the same dose using BSA calculations (Table 1), subsequent treatment should be decreased by 1 UFT capsule per day.
UFT dose reductions are expressed as a decrease in mg/m^2/day of the preceding or interrupted dose and are based on the worst grade of non-haematologic or haematologic toxicity experienced (granulocyte count or platelet count only). Retreatment within a course or at the start of the next course should be withheld until evidence of haematologic recovery (i.e. granulocyte count $\geq 1500/mm^3$ and platelet count $\geq 100,000/mm^3$) and recovery of all non-hematologic toxicities to baseline of $\leq$CTC grade I. In the event of CTC grade 2 non-haematologic toxicity, no adjustment in the UFT dose should be made. For CTC grade 3 or 4 non-haematologic toxicity, UFT is reduced by 50 mg/m^2/day for the completion of the current course and subsequent courses.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side-Effects

The following side effects have occurred in >5% patients:

Non Haematologic

Body as a whole - abdominal pain, asthenia
Gastrointestinal - diarrhoea, nausea, vomiting, stomatitis/mucositis
Hepatobiliary Elevations - SGOT, SGPT, bilirubin, alkaline phosphatase
Skin/Appendages - alopecia, discolouration, eczema, hypertrophy, leukoderma, pruritis, psoriasis, rash, pustules, Stevens-Johnson Syndrome, ulcer and vesiculobullous rash. No cases of severe hand/foot syndrome were reported.
Infection
Bleeding - haemorrhage of gastrointestinal tract, nose, urogenital tract, haemoptysis, ecchymosis and petechiae.
Peripheral Nervous System - paresthesia, neuralgia, neuropathy and hand paresis.

Haematologic

Leucopenia
Neutropenia
Febrile Neutropenia
Thrombocytopenia
Anemia

The following have occurred less frequently (1-5% of patients). Intestinal obstruction, dehydration, back pain, dyspnoea, anorexia, constipation, pain, peripheral oedema, arthralgia, weight loss, confusion, cachexia, deep thrombophlebitis and heart arrest.
The following have occurred rarely (<1% of patients). Arrhythmia, congestive heart failure, myocardial infarction, shock, enteritis, hepatitis, liver failure, gastritis, ileitis, intestinal perforation and abnormal kidney function.
Postmarketing reports have described clinically important events with single-agent UFT, however, the relevance of these reports describing single- agent UFT therapy to experience with UFT/calcium folinate is not clear. The following additional clinically relevant adverse events have been received in postmarketing reports for single-agent UFT:
Body as a Whole: malaise, photosensitivity.
Cardiovascular System: angina.
Digestive System: acute pancreatitis, hepatic cirrhosis, fulminant hepatitis, gastric/duodenal ulcer.
Nervous System: disturbances of consciousness, extrapyramidal symptoms, gait disturbance, leukoencephalopathy, memory loss, paralysis in the extremities, speech disturbance.
Respiratory System: interstitial pneumonia.
Skin and Appendages: discoid lupus erythematosus-like eruption, skin dyscrasis (including nail abnormalities, blistering, and dermatitis), urticaria.
Special Senses: anosmia.
Urogenital System: acute renal failure, nephrotic syndrome, urinary incontinence.

PRECAUTIONS

General

Patients receiving UFT/calcium folinate should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Most side effects are reversible and don't require permanent discontinuation, although doses may need to be withheld or reduced (see DOSAGE AND DIRECTIONS FOR USE.)

Heart Disease

UFT/calcium folinate should be used with caution in patients with a history of heart disease.
Myelosuppression: UFT administration may use myelosuppression in some patients.
Renal Insufficiency: There is little experience with UFT in patients with renal impairment. Physicians should exercise caution when UFT is administered to such patients. (See PHARMACOLOGICAL ACTION)
Hepatic Insufficiency: Patients with mild to moderate hepatic dysfunction should be carefully monitored by liver

function tests when UFT is administered.
Symptoms of Bowel Obstruction: Oral medications, including UFT, should be used with caution in patients with symptoms of bowel obstruction.

Geriatric Use

In general, treatment for elderly patients should be given cautiously, because of the possibility of decreased hepatic, renal or cardiac function, the presence of concomitant disease and the use of other medication.
Interactions with medication metabolised by Cytochrome P450 Enzymes: Tegafur is metabolised to some extent by human cytochrome P450 2A6. UFT should therefore be administered with caution when used concomitantly with other medications that are substrates or inhibitors of CYP2A6. (See also METABOLISM under PHARMACOLOGICAL ACTION)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage could lead to fatal complications. Anticipated manifestations might include nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding, bone marrow suppression (including leukopenia, thrombocytopenia and agranulocytosis). No specific antidote is available, supportive care should be administered.

IDENTIFICATION

UFT capsules are opaque, white, hard gelatin capsules (size 2) with the code TC 434 imprinted in beige on them. Contents are white granules and/or white powder.

PRESENTATION

Opaque, white, square, plastic bottles with child-resistant closures, containing 100 capsules.

STORAGE INSTRUCTIONS

Store at temperatures not exceeding 25°C. Procedures for the proper handling and disposal of anti-cancer medication should be followed.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

34/26/0398

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