UFUR Capsule

UFUR contains tegafur and uracil in a molar ration of 1:4, and is an antimalignant tumor agent with antimetablolic effect.

Tegafur is an antitumor agent synthesized in 1966 by Dr. Hiller,S.A. et al. It is gradually converted to 5-fluorouracil (5-FU) in vivo to show it's efficacy, and is a prodrug of 5-FU. Conversely, uracil is a compound of nucleic acids and shows hardly any pharmacological and toxic effects when singly administered.

It was confirmed in basic studies that tegafur and uracil in a molar ration of 1:4 suppressed the catabolism of 5-FU (a metabolite of tegafur), increased selectively the levels of active antitumor compounds in tumors, thereby enhancing its effects. In clinical trials the product was confirmed to have an optimal combination ratio, with long lasting characteristics and a high concentration of 5-FU levels in tumor. It shows efficacy as an antitumor agents in the treatment of the following cancers: gastric cancer, colorectal cancer and breast cancer.

【Composition】

UFUR：Each capsule contains 100mg of tegafur and 224mg of uracil.

【Indications】

UFUR capsule is indicated to remission of subjective and objective symptoms in the following cancers: head and neck, gastric, colorectal, liver, gallbladder or bile-duct, pancreatic, lung, breast, bladder, prostatic, and uterine cervical.
Folinate plus Tegafur-Uracil combination therapy is indicated for colorectal cancer.

Under physician's prescription

【Dosage and administration】

UFUR capsules are administered orally. The usual dosage is (Tegafur : 300 – 600mg) 3 – 6 capsules daily in 2 -3 divided doses. For patients with cervical cancer, the usual dosage in 6 capsules (Tegafur 600mg) daily in 2 -3 divided doses. Even in combination chemotherapy with other antineoplastics, the drug is given as described above.

[Dose Calculation Table]

	Typical daily dose	
Tegafur-equivalent dose	300~600mg	Uterine cervical cancer: 600mg
Number of UFUR capsule	3~6 capsules	6 capsules

Folinate plus Tegafur-Uracil combination therapy

For colorectal cancer, Tegafur-Uracil is to be administered at a typical daily dose equivalent to 300-600 mg tegafur (the standard rate: equiv. 300 mg tegafur /m^2) orally in three divided doses (at an interval of approx. 8 hours) more than 1 hour before or after meal. A typical daily dose of Folinate is 75 mg for adults, administered orally in three divided doses (at an interval of approx. 8 hours) together with Tegafur-Uracil. Repeat a course of a consecutive 28-day administration period followed by a 7-day rest period.

Precautions on Dosage and Administration

Folinate plus Tegafur-Uracil combination therapy

1. Meals affect the efficacy of Folinate plus Tegafur-Uracil combination therapy. Administration should be withheld during one hour before or after meal.
2. See the standard administration schedule shown below:

Body surface area (m^2)	UFUR (mg/day)	Daily schedule (mg)		
		Morning	Afternoon	Night
<1.17	300	100	100	100
1.17-1.49	400	200	100	100
1.5-1.83	500	200	200	100
> 1.83	600	200	200	200

【Warnings】

1. The concomitant use of a fluorouracil-group drug with the antiviral drug, sorivudine, has been reported to cause serious blood dyscrasis, which is fatal in some cases. Do not use any fluorouracil-group drug in combination with sorivudine.
2. Because there may occur severe liver dysfunction, such as fulminant hepatitis, patients' hepatic function should be monitored closely by regular laboratory examinations. If abnormalities are found, discontinue administration and take proper treatments immediately.
3. This drug should not be combined with Tegafur, Gimeracil and Oteracil potassium combination product because the concomitant administration with this combination product may cause adverse reactions such as serious blood dyscrasia
4. Folinate plus Tegafur-Uracil combination therapy
   (1) This combination therapy is designed to enhance cytotoxicity of Tegafur-Uracil, and has been associated with fatal cases, This therapy should be performed by an experienced chemotherapist in a medical facility well equipped for emergencies.
   (2) This combination therapy may cause serious diarrhea, sometimes leading to fatal outcome. Patient should be closely monitored and, if symptoms of severe abdominal pain or diarrhea develop, immediately discontinue the chemotherapy and take proper measures. Dehydration should be managed with fluid replacement or other appropriate treatment.
   (3) This combination therapy may cause serious hepatic damage including fulminant hepatitis, or serious bone marrow depression, sometimes leading to fatal outcome. Hepatic and hematologic parameters of patients should be monitored on a regular basis (at least once a course, and additional tests prior to first and second courses) for early signs of such damages. Be alert for problem and complaints signaling hepatic damages such as malaise with accompanying anorexia. If jaundice or a yellow sclera appears, discontinue administration immediately and take proper measures.

【Precautions】

1. General Precautions

(1). Because there may occur severe adverse reactions such as bone marrow depression, patients' hematological, hepatic, and renal function should be monitored closely by frequent laboratory examinations. If abnormalities appear, proper treatments should be taken such as dose reduction or discontinuation. Long-term administration should be conducted with great caution because of the potentiality of severe and delayed adverse reactions.

(2). Because there may occur severe liver dysfunction, such as fulminant hepatitis, patients' hepatic function should be monitored closely by regular laboratory examinations, especially in the early stage of administration to detect the liver damage as early as possible. Close monitoring should be given to detect possible fatigue accompanied by anorexia, which is thought to be a signal or subjective symptom of liver

dysfunction. If jaundice (yellow ocular coloring) appears, discontinue administration immediately.

(3). There may occur dehydration and severe enteritis (hemorrhagic enteritis, ischemic enteritis, necrotic enteritis, etc.). Accordingly, close observation is necessary. If severe symptoms appear such as severe abdominal pain or diarrhea, discontinue administration and take proper treatments. In case of dehydration, proper fluid supplementation should be taken.

(4). Care should be taken to avoid the manifestation or progression of infections or bleeding tendencies.

(5). The concomitant use of the antiviral drug sorivudine and the fluorouracil-group drug (tegafur, doxifluridine, 5-FU, etc.) may cause severe hematological disease by the inhibition of the metabolism of fluorouracil-group drug. The result may be serious blood dyscrasia. Accordingly, be sure that the patient is not given sorivudine when any fluorouracil-group drug is used.

(6). Administration to children should be conducted with great caution, paying attention to manifestations of adverse reactions.

(7). Administration to children and reproducible patients should be performed with consideration of potential gonadic effects.

(8). Folinate plus Tegafur-Uracil combination therapy

1). This combination therapy may cause serious diarrhea or enteritis, sometimes leading to fatal outcome. Patients should be closely observed and if symptoms of severe abdominal pain or diarrhea develop, discontinue the chemotherapy and take proper measures. Dehydration should be managed with fluid replacement or other appropriate treatments.

2). This combination therapy may cause fulminant hepatitis or serious bone marrow depression, sometimes leading to fatal outcome. The patient's conditions should be closely observed by regular monitoring of hepatic and hematologic parameters (at least once a course, plus additional tests prior to first and second courses). If any abnormalities are detected, take appropriate measures, eg, dose reduction or withdrawal.

2. Contraindications (this product is contraindicated to the following patients.)

(1). Patients with severe hypersensitivity history to the ingredients of this product.

(2). Patients in sorivudine therapy. (The concomitant use of a fluorouracil-group drug with the antiviral drug sorivudine to cause severe blood dyscrasia, which is fatal in some patients, has been reported.)

3. Careful administration (This product should be administered with caution in the following patients.)

(1). Patients with bone marrow depression. (Aggravation of bone marrow depression may occur.)

(2). Patients with hepatic dysfunction. (Exaggeration of adverse reactions may occur.)

(3). Patients with renal dysfunction. (Exaggeration of adverse reactions may occur.)

(4). Patients with infectious diseases. (Aggravation of infectious disease may occur as a result of potential bone marrow depression.)

(5). Patients with varicella. (Fatal systemic disease may occur.)

(6). Patients with gastric/duodenal symptoms. (Aggravation of symptoms may occur.)

(7). Patients with glucose intolerance. (Glucose intolerance may be aggravated.)

(8). Patients with heart disease or a history of heart disease

(9). Elderly patients

(10). Patients on other chemotherapy or radiotherapy (Diarrhea, bone marrow depression or other adverse reactions may be aggravated)

(11). Patients previously treated with other chemotherapy.

4. Drug Interactions

(1). Tegafur, Gimeracil and Oteracil potassium combination product: Serious blood dyscrasia and gastrointestinal disorder such as diarrhea and stomatitis may occur early when coadministered with Tegafur, Gimeracil and Oteracil potassium combination product. This drug should not be administered during the administration of this combination product or within at least 7 days after withdrawal of this combination.

(2). Warfarin potassium: Since the effect of warfarin potassium may be enhanced by tegafur, caution should be exercised with respect to fluctuation of coagulating ability.

(3). Contraindicated coadministration

Sorivudine. (Combined the antiviral drug sorivudine with fluorouracil-group drug (tegafur, doxifluridine, and 5-FU) may inhibit the metabolism of fluorouracil-group drug, resulting in elevated blood concentration, which may cause an adverse drug reaction such as severe blood dyscrasia.)

(4). Careful coadministration

1). Phenytoin (The action of phenytoin may be intensified by this product.)

2). Other antimalignant tumor agents or radiation therapy. (Exaggerated adverse reactions might occur, such as bone marrow depression.)

5. Adverse Reactions (rarely: <0.1%, infrequently: 0.1%~<5%, no specific designation: frequency unknown)

(1). Severe adverse reactions

1). Bone marrow depression such as pancytopenia or agranulocytosis. Pancytopenia or agranulocytosis may occur rarely. Anemia, leucopenia, thrombocytopenia, or bleeding tendency may occur infrequently. Accordingly, patients should be closely monitored by regular blood examinations (especially frequent in the early stage of administration). If abnormalities appear, take proper treatments such as discontinue administration.

2). Severe liver dysfunction

Severe liver dysfunction such as fulminant hepatitis may occur rarely. Accordingly, patients should be closely monitored by regular liver function test (especially frequent in the early stage of administration). If abnormalities appear, discontinue administration and take proper treatments.

3). Dehydration

If severe diarrhea occurs, discontinue administration and take proper treatments as fluid replacement.

4). Severe enteritis

Hemorrhagic enteritis, ischemic enteritis, or necrotic enteritis may occur. Accordingly, patients should be monitored closely. If severe abdominal pain or diarrhea occurs, discontinue administration and take proper treatments.

5). Leukoencephalopathy

Somnolence, consciousness disturbance, sensory disturbance, extrapyramidal symptoms, urinary incontinence, tetraplegia, speech disorder, gait disturbance, disturbed orientation, or hypomensia that leads to leukoencephalopathy may occur rarely. Precursors of such symptoms are dizziness/light headed feeling, numbness, impaired tongue movement, gait tripping, or forgetfulness. Patients should therefore be closely monitored. Discontinue administration if any such abnormalities appear.

6). Anosmia

Anosmia may occur rarely. Accordingly, patients should be monitored closely. If abnormalities appear, discontinue administration and take proper treatments.

7). Interstitial pneumonia

Interstitial pneumonia may occur rarely. Accordingly, patients should be monitored closely. Discontinue administration if abnormalities appear, and take proper treatments.

8). Silence angina

Silence angina may occur rarely. Accordingly, patients should be monitored closely. Discontinue administration if abnormalities appear, and take proper treatments.

(2). Other adverse reactions

1). Liver

Jaundice and elevation of GOT or GPT may occur infrequently. Fatty liver may occur rarely. Accordingly, patients should be monitored closely. If abnormalities appear, take proper treatments such as discontinuation of administration.

2). Kidney

Proteinuria or hematuria may occur rarely. Increased BUN or creatinine may occur infrequently. Accordingly, patients should be monitored closely. If abnormalities appear, take proper treatments such as discontinuation of administration.

3). Gastro-intestine

Anorexia, nausea, vomiting, diarrhea, stomatitis, epigastric pain, abdominal pain, gastric/duodenal ulcers, heart burn, abdominal distension, taste abnormality, or gastritis may occur infrequently. Angular stomatitis, glossitis, borborygmus, dry mouth, constipation, difficult swallowing or gastrointestinal hemorrhage may occur rarely. Accordingly, patients should be monitored closely. If abnormalities appear, take proper treatments such as dose reduction or discontinuation of administration. Discontinue administration if ulcer or hemorrhage occurs.

4). Psychoneurologic system

Malaise or vertigo may occur infrequently. Headache, excitement or tinnitus may occur rarely.

5). Skin

Skin abnormalities may occur infrequently, such as pigmentation, keratosis, nail abnormality, blisters, erosion or dermatitis (which tend to develop on the palms or soles), as well as edema or alopecia. Flushing, SLE-like eruption, or photosensitive reactions may occur rarely. Accordingly, patients should be closely monitored. If abnormalities appear, take proper treatments such as discontinuation of administration.

6). Pancreas

Acute pancreatitis may occur rarely. Accordingly, patients should be monitored closely. If abdominal pain or an elevation of serum amylase and lipase appears, take proper treatments such as discontinuation of administration.

7). Hypersensitivity

Rash or itching may occur infrequently. Urticaria may occur rarely. Discontinue administration if abnormalities appear.

8). Cardiovascular

Distressed feeling of chest, chest pain, or abnormal ECG (ST elevation, etc.) may occur rarely.

9). Others

Fever may occur infrequently. Cough/sputum, arthralgia, glycosuria, burning sensation, bloody sputum, or conjunctival congestion may occur rarely.

6. Use in the elderly

Care should be exercised in administration to elderly patients whose physiological functions are generally in a diminished state.

7. Use during pregnancy or lactation

(1). Teratogenicity as reported in animal (rats) experiments. This product should therefore not be administered to patients who are or may be pregnant.

(2). Transfering to milk is reported in animal (rats) experiments. Accordingly, avoid administration to nursing women. If medication is unavoidable during lactation, the patient should discontinue nursing.

8. Pediatric use

The safety of this product in children has not been established.

9. Others

It is reported that changes have been observed in cerebral tissues, such as in the columna fornicis and the commissura anterior, during long-term (nine-months) administration of high dose to dogs.

10. Symptoms and treatment of overdose

Signs and symptoms are qualitatively similar to the side effects. Treatment should be performed promptly and appropriate drugs are given to control symptoms of overdosage.

【Pharmacology】

1. Antitumor activity

This product has effects to inhibit the growth of tumors such as Walker-256 carcinosarcoma, Yoshida's sarcoma, ascitis carcinoma (in rats), Sarcoma-180, Ehrlich's carcinoma, Lewis's lung arcinoma, and B-16metanoma (in mice) transplanted subcutaneously. This product also has effects to inhibit the growth of human cancers such as gastric, beast, and pancreatic when transplanted subcutaneously to nude mice. This product also has survival effects in animals (mice) bearing L-1210 transplanted leukemia.

2. Mechanism of action

The antitumor activity of this product is based on 5-FU that appears gradually in the body via the transformation of tegafur. The action mechanism of 5-FU is considered to be inhibition of DNA synthesis resulting from the antagonistic effect of the active metabolite FdUMP, which antagonize dUMP and inhibit thymidylate synthase. The function of RNA

will be disordered according to the incorporation of FUTP into RNA (in vitro study).

Uracil, when combined with tegafur, enhances the tegafur's antitumor activity. Because 5-FU degradation is depressed by the difference of affinities to phosphorylative or degradative enzymes between 5-FU and uracil, concentrations of 5-FU and its phosphorylated active metabolite can be highly maintained in tumor tissues (in vitro).

【Pharmacokinetics】

Three capsules of this product (corresponding to 300mg as tegafur were orally administered to cancer patients, and the blood level of tegafur was maximum of 13.7±1.1μg/ml at 2 hours, which then fell gradually to 3.6±0.8μg/ml at 24 hours postadministration. The mean blood levels of 5-FU and uracil were a maximum of 0.21± 0.094μg/ml and 3.0±1.8μg/ml at 30 minutes, respectively. The level of 5-FU then fell to 0.05±0.019μg/ml at three hours, and the level of uracil fell to 0.30 ± 0.23μg/ml at six hours after administration.

Conversely, the levels of 5-FU in the blood, tumor tissues, and normal tissues adjacent to the tumors postadministration of the product were comparatively determined, from which it was realized that the 5-FU level in the tumors was the highest.

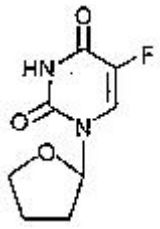
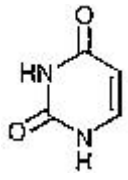
Folinate plus Tegafur-Uracil combination therapy

Influence of meals: In a cross-over trial with cancer patients, folinate (30mg) and Tegafur-Uracil (equiv. 200mg tegafur) were administered during fasting or after meal (high-fat diet). In post-prandial administration, the AUCs for Uracil and tegafur-derived fluorouracil were lower by 66% and 37%, respectively, than in fasting administration, while AUC for folinate was higher by 61%. The AUC of tegafur, on the other hand, showed no significant difference.

【Description】

White to off-white "No.2" capsule, imprinted with red 'UFUR' on both body and cap, filled with white to pale yellow granules or fine powder.

Physicochemical properties of the active ingredients

Name of active ingredients	tegafur	uracil
Structure		
Chemical name	1-(2-tetrahydrofuryl)-5-fluorouracid 5-fluoro-1-(2-tetrahydrofuryl)-2,4(1H,3H)-pyrimidinedione〔IUPAC〕	2,4(1H,3H)-pyrimidinedione
Molecular formula	$C_8H_9FN_2O_3$	$C_4H_4N_2O_2$
Molecular weight	200.17	112.09
Melting point	166~171℃	Approximately 335 ℃ (decomposition)
Description	Tegafur occurs as a white crystalline power. It is soluble in methanol, sparingly soluble in water and ethanol, and slightly in ether. It is soluble in dilute sodium hydroxide test solution.	Uracil occurs as a white crystal or crystalline power free of order or taste. It is slightly soluble in water; very slightly soluble in methanol, ethanol and acetone; and practically insoluble in ethyl acetate and chloroform.

【Storage and handling】

Regulatory classification - Cytotoxin

Storage – Store at room temperature (under 30℃)

Expiration date – Use before the expiration date on the label or package

【Package】

Packaging available 70 capsules (10 x 7 blister) per box

【Manufacturer】

TTY Biopharm Company Limited Chungli Factory

【Address】

Factory - 838, Chung Hwa Rd., Sec. 1, Chungli Dist., Taoyuan City, 32069, Taiwan

【Telephone】

0800 086 288

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