

IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0654/017/001

Case No: 2072309

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Merck Serono Limited

Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

UFT 100mg/224 mg hard capsules

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/03/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

UFT 100mg/224 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg tegafur and 224 mg uracil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

The capsules are white, opaque and imprinted with the code TC434.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

UFT is indicated for first-line treatment of metastatic colorectal cancer in combination with calcium folinate (see section 5.1).

4.2 Posology and method of administration

Adults: the dose of UFT is 300 mg/m2/day tegafur and 672 mg/m2/day uracil combined with 90 mg/day oral calcium folinate, given in three divided doses (preferably every 8 hours). Calcium folinate should be taken at the same time as UFT. Doses should be taken at least one hour before or one hour after meals for 28 consecutive days. Subsequent cycles should start after 7 days without UFT/calcium folinate (i.e. 35 days per treatment cycle). The daily dose per body surface area (BSA) is presented below:

BSA (m2)	UFT (capsules/day)	Daily schedule (number of capsules)		
		Morning	Midday	Evening
< 1.17	3	1	1	1
1.17 - 1.49	4	2	1	1
1.50 - 1.83	5	2	2	1
> 1.83	6	2	2	2

Dose modification: to manage toxicity, the following dose reduction and stopping guidelines are provided:

	Worst Common Toxicity Criteria (CTC) Grade Toxicity	UFT Dose Modification [†]
Non-Haematologic Toxicity (including diarrhoea)	0 - 1	No change
	2	Therapy withheld until toxicity resolves to ≤ grade 1. No change in subsequent dose

	3 - 4	Therapy withheld until toxicity resolves to ≤ grade 1. Decrease subsequent dose by 1 capsule/day. Dose reduction maintained for ongoing cycle and remainder of therapy
Haematologic Toxicity (based on granulocyte or platelet count)	0 - 1	No change
	2 - 4	Therapy withheld until granulocytes ≥ 1500/mm ³ and platelets ≥ 100,000/mm ³
Haematologic Toxicity: Retreatment	0 - 2	No change
	3 - 4	Decrease subsequent dose by 1 capsule/day. Dose reduction maintained for ongoing cycle and remainder of therapy

† Calcium folinate dose remains unchanged, even if < 3 UFT capsules/day are required. If UFT therapy is interrupted, calcium folinate must also be stopped. When UFT therapy is interrupted, doses that are missed during 28 consecutive days of treatment should not be taken later.

Adolescents, children, and infants: the safety and efficacy of the UFT and calcium folinate combination has not been established and should not be used in these patient populations (see section 4.3).

Elderly: the elderly population has been well studied as 45% of patients studied were at least 65 years old and 26% of these were at least 75 years old. However, elderly patients should be monitored for age-related impaired renal-, hepatic- or cardiac function or for concomitant medications or diseases (see sections 4.4 and 4.8).

Renal impairment: the effect of renal impairment on the excretion of UFT has not been assessed. Although the primary route of elimination for UFT is not renal, caution should be exercised in patients with impaired renal function. These patients should be monitored closely for any emergent toxicities (see section 4.4).

Hepatic impairment: the effect of hepatic impairment on the elimination of UFT has not been assessed (see sections 4.3 and 4.4).

4.3 Contraindications

UFT is contraindicated in patients who:

- have a known hypersensitivity to 5-FU, tegafur, uracil, or any of the excipients;
- are pregnant or attempting to become pregnant;
- are breast feeding;
- are adolescents, children or infants;
- have severe hepatic impairment;
- present with evidence of bone marrow suppression from previous radiotherapy or antineoplastic agents;
- have a known deficiency of hepatic CYP2A6;
- have a known or suspected dihydropyrimidine dehydrogenase deficiency;
- are treated or have recently been treated with dihydropyrimidine dehydrogenase inhibitors such as brivudine (see section 4.5).

4.4 Special warnings and precautions for use

Patient compliance with oral therapy: the physician should instruct the patient on the importance of full compliance with the posology and method of administration of this medicinal product. Specific guidance on the importance of following physician recommendations for dose reductions or treatment interruptions in cases of emerging toxicities should be provided (see sections 4.2 and 4.8). Individual patient characteristics that may negatively impact on this compliance should be considered in the selection of therapy for this disease.

Patients receiving the UFT/calcium folinate combination should be monitored by a physician experienced in the use of cytotoxic agents and who has the facilities for regular monitoring of clinical, biochemical and haematological effects during and after administration of chemotherapy. Any emergent toxicity should be handled as described in dose modifications (see section 4.2).

The UFT/calcium folinate combination should be used with caution in patients with, renal or hepatic impairment, signs and symptoms of bowel obstruction and in elderly patients.

Patients treated with coumarin anticoagulants (such as warfarin) concomitantly with UFT should be monitored regularly for alterations in prothrombin time or International Normalised Ratio.

Patients taking phenytoin concomitantly with UFT should be regularly monitored for increased phenytoin plasma concentrations.

Hepatic disorders: since hepatic disorders, including fatal fulminant hepatitis, have been reported in patients receiving single agent UFT, appropriate testing should be performed on any patient receiving the UFT/calcium folinate combination who presents signs and symptoms of hepatitis, other liver disease or hepatic impairment. Liver function should be monitored during treatment in patients with mild to moderate hepatic dysfunction.

Renal insufficiency: there is no experience with the UFT/calcium folinate combination in patients with renal impairment. Physicians should exercise caution when UFT/calcium folinate is administered to such patients.

Diarrhoea: UFT/calcium folinate often induces diarrhoea, however, this is mild in the majority of cases. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement to avoid the potentially fatal complications of dehydration (see section 4.2). Special attention should also be paid to the requirement to withhold therapy with UFT/calcium folinate upon occurrence of grade 2 or worse diarrhoea.

Significant cardiac disease: caution should also be exercised in patients with a history of significant cardiac disease as myocardial ischaemia and angina have been associated with fluoropyrimidine-based therapy and rare cardiac events of uncertain causality, including myocardial infarction, have been reported in patients receiving UFT.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions of UFT with other concomitantly administered medications have not been formally investigated.

Co-administration of 5-fluorouracil or its pro-drugs with medicinal products that inhibit dihydropyrimidine dehydrogenase, an enzyme responsible for the catabolism of endogenous and fluorinated pyrimidines, may lead to increased fluoropyrimidine toxicity which is potentially fatal. Therefore, UFT must not be co-administered with dihydropyrimidine dehydrogenase inhibitors such as brivudine. In patients treated with brivudine, a time interval of 4 weeks must be respected before administration of UFT to allow for recovery of enzyme activity.

Marked elevations in prothrombin time (PT) or International Normalised Ratio (INR) have been reported in patients stabilised on warfarin therapy following initiation of UFT therapy.

Increased phenytoin plasma concentrations resulting in symptoms of phenytoin intoxication have been reported with the concomitant use of UFT and phenytoin (see section 4.4).

In vitro, tegafur is partially metabolised by CYP2A6 (see section 4.3). UFT should be administered with caution in combination with substrates or inhibitors of this enzyme, e.g. coumarin, methoxypsoralen, clotrimazole, ketoconazole, miconazole. Neither tegafur nor uracil significantly inhibits the *in vitro* activity of CYP3A4 or CYP2D6. Furthermore, *in vitro*, tegafur is not metabolised by CYP1A1, -1A2, -2B6, -2C8, -2C9, -2C19, -2D6, -2E1, or -3A4 suggesting it is unlikely that there will be interactions with medications metabolised by these enzymes.

The absorption of UFT is affected by food (see section 5.2).

4.6 Pregnancy and lactation

Pregnancy: for UFT, no clinical data on exposed pregnancies are available. Uracil/tegafur is suspected to cause serious birth defects when administered during pregnancy. UFT is therefore contraindicated (see section 4.3) in pregnancy. Contraceptive measures must be taken by both male and female patients during (and up to 3 months after) treatment. If pregnancy occurs during treatment with UFT, genetic counselling would be considered.

Male patients who are considering to father a child during or after treatment should seek advice regarding cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with UFT.

Lactation: it is not known whether tegafur, uracil, and 5-FU are excreted in human milk following UFT administration. Because of the potential for serious adverse reactions in nursing infants, the use of UFT in lactating women is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

The UFT/calcium folinate combination has not been demonstrated to interfere with the ability to drive or use machines. However, as confusion has occasionally been reported (see section 4.8), patients should be advised to exercise caution.

4.8 Undesirable effects

Unless otherwise indicated, the undesirable effect information relates to the 594 patients that have been treated with UFT/calcium folinate combination in two Phase III trials with a median of 3 to 3.5 courses (see section 5.1).

As with all cytotoxic agents, adverse reactions can be expected in the majority of patients. Most undesirable effects observed, including diarrhoea, nausea and vomiting were reversible and rarely required permanent discontinuation of therapy, although doses were withheld or reduced in some patients (see section 4.2). The most common severe and clinically relevant adverse events, regardless of attribution to UFT/calcium folinate were diarrhoea (20%), nausea/vomiting (12%), abdominal pain (12%) and asthenia (9%).

Approximately 45% of these patients were ≥ 65 years of age, and about 26% of these were ≥ 75 years. No clinically relevant differences in safety were observed, although older patients tended to have a higher incidence of anaemia, diarrhoea and stomatitis/mucositis.

The following information specifies undesirable effects of any severity, reported at a frequency of $\geq 1\%$ and attributed to UFT/calcium folinate. Additionally, terms are (*) when severe and clinically relevant undesirable effects, regardless of treatment attribution to UFT/calcium folinate, were reported in a proportion of patients at a frequency of $\geq 0.1\%$.

The following definitions apply to the frequency terminology used hereafter:

Very common ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Uncommon ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

Very rare ($< 1/10,000$)

Infections and infestations:

common: moniliasis, pharyngitis
 uncommon: infection *, sepsis *

Blood and lymphatic system disorders:

very common: myelosuppression, anaemia, thrombocytopenia, leukopenia, neutropenia
 uncommon: coagulation disorder *, febrile neutropenia

Metabolism and nutrition disorders:

very common: anorexia
 common: dehydration *, cachexia *

Psychiatric disorders:

common: insomnia, depression, confusion *

Nervous system disorders:

common: taste perversion *, taste loss, somnolence, dizziness, paraesthesia, headache

Eye disorders:

common: lacrimation, conjunctivitis

Cardiac disorders:

uncommon: arrhythmia *, congestive heart failure *, myocardial infarction *, heart arrest *

Vascular disorders:

common: deep thrombophlebitis *
 uncommon: shock *

Respiratory, thoracic and mediastinal disorders:

common: dyspnoea *, increased coughing
 uncommon: pulmonary embolism *

Gastrointestinal disorders:

very common: diarrhoea *, nausea *, stomatitis *, vomiting *, abdominal pain *
 common: constipation *, flatulence, dyspepsia, mucositis *, dry mouth, eructation, , intestinal obstruction *
 uncommon: enteritis *, gastritis *, ileitis *, intestinal perforation *

Hepato-biliary disorders:

uncommon: hepatitis *, jaundice *, liver failure *

Skin and subcutaneous tissue disorders:

common: alopecia, rash, exfoliative dermatitis, skin discolouration, pruritus, photosensitivity, sweating, dry skin, nail disorder

Musculoskeletal, connective tissue and bone disorders:

common: myalgia, back pain *, arthralgia *

Renal and urinary disorders:

uncommon: abnormal kidney function *, urinary retention *, haematuria *

Reproductive system and breast disorders:

uncommon: impotence *

General disorders and administration site conditions:

very common: asthenia^{*}

common: peripheral oedema^{*}, fever^{*}, malaise, chills, pain^{*}

uncommon: chest pain^{*}

Investigations:

very common: increased alkaline phosphatase, increased ALT, increased AST, increased total bilirubin^{**}

common: weight loss^{*}

(^{**}) Hyperbilirubinaemia was reported approximately twice as often when compared with the bolus 5-FU/calcium folinate control arm. When reported, it was usually isolated, reversible and not associated with an adverse clinical outcome.

After marketing the following additional adverse reactions, have been reported for single-agent UFT. Only those adverse reactions that are not described in the UFT plus CF clinical trial experience are noted.

Infections and infestations:

very rare: pneumonia

Neoplasms benign, malignant and unspecified (incl cysts and polyps):

very rare: myelodysplastic syndrome, acute myeloic leukaemia, acute promyelocytic leukaemia

Blood and lymphatic system disorders:

very rare: haemolytic anaemia, agranulocytosis, pancytopenia, disseminated intravascular coagulation

Nervous system disorders:

rare: anosmia, parosmia, leukoencephalopathy

very rare: memory loss, movement disorders including extrapyramidal symptoms and paralysis in the extremities, speech disturbance, , disturbance of consciousness, hypaesthesia

Cardiac disorders:

very rare: angina

Respiratory, thoracic and mediastinal disorders:

rare: interstitial pneumonia

Gastrointestinal disorders:

very rare: acute pancreatitis, gastro/duodenal ulcer, enterocolitis, ileus paralytic, ascites, ischaemic colitis

Hepato-biliary disorders:

very rare: hepatic cirrhosis, fulminant hepatitis, hepatic fibrosis^{***}

Skin and subcutaneous tissue disorders:

very rare: discoid lupus erythematosus-like eruption, skin dyscrasia (including blistering, and dermatitis), urticaria, Stevens Johnson syndrome, palmar-plantar erythrodysesthesia

Renal and urinary disorders:

very rare: acute renal failure, nephrotic syndrome, urinary incontinence

General disorders and administration site conditions:

rare: fatigue

very rare: multi-organ failure, gait disturbance

(***) Very rare cases of mild to moderate hepatic fibrosis without elevation of serum transaminase levels have been reported in patients with elevated serum 7S collagen and PIIINP levels receiving UFT alone.

4.9 Overdose

In case of overdosing, the frequency and severity of undesirable effects can increase, leading to possibly fatal conditions. Anticipated manifestations include nausea, vomiting, diarrhoea, gastrointestinal ulceration, bleeding, and bone marrow suppression (thrombocytopenia, leukopenia, and agranulocytosis). No specific antidote is available; supportive care should be provided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, pyrimidine analogues. ATC code: L01B C53.

UFT, an orally administered dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine, is a fixed molar ratio (1:4) of tegafur and uracil. Uracil is a competitive inhibitor of 5-FU degradation.

The combined individual activities of uracil and calcium folinate give rise to dual biomodulation:

- Tegafur is an oral prodrug of 5-FU and uracil reversibly inhibits DPD, the primary catabolic enzyme for 5-FU, and
- Calcium folinate enhances the cytotoxicity of 5-FU via one of its intracellular metabolites, 5,10-methylenetetrahydrofolate.

5-FU undergoes intracellular activation into its active metabolites, 5-fluoro-deoxyuridine-monophosphate (FdUMP) and 5-fluorouridine-triphosphate (FUTP). FdUMP inhibits DNA synthesis by forming inhibitory tertiary complexes with thymidylate synthetase (TS) and reduced intracellular folates. FUTP is integrated into cellular RNA, causing disruption of RNA function. Following competitive inhibition of DPD by uracil, tegafur-derived plasma concentrations of 5-FU are elevated.

The efficacy of the UFT/calcium folinate combination in metastatic colorectal carcinoma has been established in 2 randomised and comparative phase III trials vs. the Mayo regimen (IV 5-FU [425 mg/m²/day] and calcium folinate [20 mg/m²/day]) administered for 5 days every 4 weeks (study-011) or every 5 weeks (study-012).

In study -011 (n= 816), there was no statistically significant difference in the primary endpoint of survival between the two treatment arms. The median survival time was 12.4 months (95% CI: 11.2-13.6 months) and 13.4 months (95% CI: 11.6-15.4 months) in the UFT/calcium folinate and the 5FU/calcium folinate treatment groups, respectively. The hazard ratio for 5-FU/calcium folinate over UFT/calcium folinate was 0.96 (95% CI: 0.83-1.13). The assessment of the secondary endpoint of time to progression in this study was complicated by the difference in cycle duration between the two treatment arms. The median time to progression was 3.5 months (95% CI: 3.0-4.4 months) and 3.8 months (95% CI: 3.6-5.0 months) in the UFT/calcium folinate and 5-FU/calcium folinate treatment groups, respectively (p= 0.01).

In study -012 (n= 380), there was no statistically significant difference in the primary endpoint of time to progression nor in the secondary endpoint of survival between the two treatment arms. The median time to progression was 3.4 months (95% CI: 2.6-3.8 months) and 3.3 months (95% CI: 2.5-3.7 months) in the UFT/calcium folinate and 5-FU/calcium folinate treatment groups, respectively. The median survival time was 12.2 months (95% CI: 10.4-13.8 months) and 10.3 months (95% CI: 8.2-13.0 months) in the UFT/calcium folinate and 5-FU/calcium folinate treatment groups, respectively. The hazard ratio for 5-FU/calcium folinate over UFT/calcium folinate was 1.14 (95% CI: 0.92-1.42).

In the first-line treatment of metastatic colorectal carcinoma, combinations of novel agents with 5-FU have been authorised. However, the use of UFT in combination with novel agents is still under investigation.

5.2 Pharmacokinetic properties

The single dose and steady-state plasma pharmacokinetics of oral UFT have been evaluated in patients with colorectal cancer.

Absorption

Following UFT administration, tegafur and uracil are rapidly absorbed. C_{\max} of tegafur, uracil, and 5-FU were achieved within 1 to 2 hours. Concurrent administration of oral calcium folinate with UFT did not significantly alter the plasma pharmacokinetics of tegafur, uracil, or 5-FU. Similarly, UFT did not affect the absorption of oral calcium folinate. Following a high-fat meal, plasma AUC for uracil and 5-FU were 66% and 37% lower, respectively, compared with UFT under fasting conditions. Plasma tegafur AUC was not significantly altered. C_{\max} was reduced and delayed for tegafur, uracil, and 5-FU.

Distribution

Following oral administration of UFT, plasma concentrations over time for UFT and uracil generally display monoexponential absorption and elimination processes. The mean apparent oral volume of distribution for tegafur and uracil following UFT dosing at steady state are 59 and 474 L, respectively. Serum protein binding is 52% for tegafur but negligible for uracil.

Metabolism

Conversion of tegafur to 5-FU occurs via C-5' oxidation (microsomal enzymes) and C-2' hydrolysis (cytosolic enzymes). Microsomal oxidation of tegafur is partially mediated by CYP2A6. The cytosolic enzymes responsible for the metabolism of tegafur are not known. Other metabolic products of tegafur include 3'-hydroxy tegafur, 4'-hydroxy tegafur, and dihydro tegafur which are all significantly less cytotoxic than 5-FU. The metabolism of 5-FU formed from tegafur follows the intrinsic *de novo* pathways for the naturally occurring pyrimidine, uracil.

Neither tegafur, uracil or 5-FU inhibited the catalytic conversion of cDNA-derived cytochrome P450 CYP1A2, -2C9, -2C19, -2D6 and -3A4 at concentrations of at least 100 μM . This data suggests that UFT is unlikely to significantly alter the metabolic clearance of drugs metabolised by these routes.

Elimination

Less than 20% of tegafur is excreted intact into the urine. The terminal elimination half-lives of tegafur and uracil following UFT are approximately 11 hours and 20-40 minutes, respectively. The three hydroxy metabolites of tegafur are excreted in the urine. The plasma half-life for S-tegafur (10.3 hours) is 4.4 times longer relative to R-tegafur (2.4 hours).

Following UFT 300 $\text{mg}/\text{m}^2/\text{day}$, in three divided doses, tegafur plasma concentrations of $> 1,000 \text{ ng/ml}$ are maintained, whereas uracil concentrations decline rapidly following C_{\max} 5-FU plasma concentrations peak in 30 to 60 minutes at approximately 200 ng/ml , and remain detectable ($> 1 \text{ ng/ml}$) over each 8-hour dosing interval. No significant accumulation of tegafur, uracil or 5-FU occurred over a 28-day course of UFT therapy.

Linearity/Non-Linearity

Following single dose UFT (100 to 400 mg), increases in plasma exposures (C_{\max} and AUC) of tegafur were generally in proportion to dose. Increases in uracil and 5-FU plasma exposures were greater than in proportion to dose.

Pharmacokinetics in Special Populations

A pooled statistical analysis of single dose UFT (200 mg) pharmacokinetic data (C_{\max} and AUC) from three studies (46 patients, average age 60 years, 28 male, 18 female) did not identify clinically significant associations between patient age, gender and presence of metastatic liver involvement and the pharmacokinetics of tegafur, uracil or 5-FU following single dose UFT. In view of the predominant reliance of hepatic processes for the metabolism and elimination of both tegafur and uracil, renal abnormalities are unlikely to have significant effect on the pharmacokinetics of UFT.

5.3 Preclinical safety data

In rats and dogs, repeated dosing with UFT produces toxicity in the gastrointestinal tract, lymphoid organs, bone marrow, liver, kidney and testes. Round vacuoles, were observed histologically in the cerebrum of dogs that did not exhibit any clinical signs. With the exception of testicular changes and the vacuoles in the cerebrum of dogs, all of these findings were reversible.

Following UFT administration, tegafur, uracil and 5-FU are excreted in breast milk in rats. Also in rats, UFT showed maternal toxicity and a decrease in conception rate. Embryomortality, foetal toxicity and teratogenicity were observed in rats, mice and rabbits. UFT was not mutagenic in bacterial strains but did induce chromosomal aberrations in Chinese Hamster Ovary cells and was genotoxic in a rat micronucleus test. Long-term animal carcinogenicity studies have not been conducted. However, the positive mutagenicity data are indicative of a carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Low-substituted hydroxypropylcellulose, sodium laurilsulfate.

Capsule shell: gelatin and titanium dioxide (E171).

Capsule shell imprints (edible ink): titanium dioxide (E171), synthetic iron oxide red (E172), carnauba wax, shellac and glyceryl monooleate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters.

Packs of 21, 28, 35, 36, 42, 56, 70, 84, 112, 120, 140, 144 (4x36) or 168 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Procedures for the proper handling and disposal of cytotoxic drugs should be followed.

7 MARKETING AUTHORISATION HOLDER

Merck Serono Limited
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Stanwell Road
Feltham
Middlesex
TW14 8NX
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 654/17/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 December 2000

Date of last renewal: 23 March 2010

10 DATE OF REVISION OF THE TEXT

August 2010