Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 25 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of the solution contains 25 mg of fluorouracil (present as sodium salt).

Excipient with known effect
The 10ml vial contains 40.1 mg of sodium in each vial.
The 20ml vial contains 80.2 mg of sodium in each vial.
The 100ml vial contains 401 mg of sodium in each vial.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless or slightly yellow solution without visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil may be used alone or in combination, for its palliative action in the management of common malignancies particularly cancer of the colon and breast.

4.2 Posology and method of administration

Method of administration

Selection of an appropriate dose and treatment regime depends upon the condition of the patient, the type of carcinoma being treated and whether fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with the patient's actual bodyweight unless there is obesity, oedema or some form of abnormal fluid retention such as ascites. Ideal weight is used as the basis for calculation in such cases.
Fluorouracil may be used in combination with other cytotoxic chemotherapeutic agents; however, fluorouracil injection should not be mixed directly in the same container with other chemotherapeutic agents or intravenous additives.

Fluorouracil Injection BP can be given by intravenous injection or infusion or intra-arterial regional perfusion.

Fluorouracil is often administered concomitantly with calcium folinate (folinic acid) which may potentiate the therapeutic effects of fluorouracil. Therefore, the toxicity of fluorouracil, especially GI and hematologic, may be increased. Careful monitoring should be observed and the dose of fluorouracil may be decreased based on current guidelines (see section 4.5).

Posology

Adults:

The following regimen have been recommended for use as a single agent:

Initial Treatment:

This may be in the form of an infusion or an injection, the former usually being preferred because of lesser toxicity.

Intravenous Infusion:

15 mg/kg bodyweight but not more than 1 g per infusion diluted in 300 – 500 ml of 5% glucose or 0.9% sodium chloride injection given over 4 hours. Alternatively the daily dose may be infused over 30 - 60 minutes or may be given as a continuous infusion over 24 hours. The infusion may be repeated daily until there is evidence of toxicity or a total dose of 12 – 15 g has been reached.

Intravenous Injection:

12 mg/kg bodyweight may be given daily for 3 days and then, if there is no evidence of toxicity, 6 mg/kg on alternate days for 3 further doses. An alternative regimen is 15 mg/kg as a single intravenous injection once a week throughout the course.

Intra-arterial Infusion:

5 - 7.5 mg/kg bodyweight daily may be given by 24 hour continuous intra-arterial infusion.

Maintenance Therapy:

An initial intensive course may be followed by maintenance therapy providing there are no significant toxic effects. In all instances, toxic side effects must disappear before maintenance therapy is started.

The initial course of fluorouracil can be repeated after an interval of 4 to 6 weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5 – 15 mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30 g at a maximum rate of 1 g daily.

A more recent alternative method is to give 15 mg/kg IV once a week throughout the course of treatment. This obviates the need for an initial period of daily administration.

In Combination with Irradiation

Irradiation combined with 5-FU has been found to be useful in the treatment of certain types of metastatic lesions in the lungs and for the relief of pain caused by recurrent, inoperable growth. The standard dose of 5-FU should be used.

Dose reduction in certain situations

The initial dose should be reduced by one-third to one half in patients with any of the following:
1. Cachexia.
2. Major surgery within preceding 30 days.
3. Reduced bone marrow function.

If the leukocyte count is < 2.5 x 10^9/l and/or the thrombocyte count is < 75 x 10^9/l, the treatment should be discontinued for one week. If the blood count is normalized during this period of time, the treatment can be resumed. In other cases the dosage is as follows:

Leukocytes (x 10^9/l)	**Thrombocytes (x 10^9/l)**	**Dosage**
> 3.5	> 125	Recommended dose
2.5 - 3.5	75 - 125	50% of the recommended dose
< 2.5	< 75	Suspend treatment.

4. Impaired hepatic or renal function.

If plasma bilirubin concentration is >5 mg/dl, treatment with fluorouracil should be discontinued. If the patient's hepatic or renal function is impaired, the recommended dose can be reduced by 30 to 50% (see sections 4.4 and 5.2).

Paediatric Population

No recommendations are made regarding the use of fluorouracil in children.

Elderly:

Fluorouracil should be used in the elderly with similar considerations as in younger adults, notwithstanding that the incidence of concomitant medical illness is higher in the former group.

4.3 Contraindications

Fluorouracil is contraindicated in patients who;

- Have known hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Are suffering from potentially serious infections (e.g. Herpes zoster, chickenpox)
- Are seriously debilitated
- Have a poor nutritional state
- Are suffering from bone marrow depression after radiotherapy or treatment with other antineoplastic agents
- Have serious liver impairment
- Have known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4)
- Have been treated with brivudine, sorivudine or their chemically related analogues,which are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD) (see sections 4.4 and 4.5) . Fluorouracil must not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues
- Fluorouracil (5-FU) must not be given to patients homozygotic for dihydropyrimidine dehydrogenase (DPD)
- Are breast feeding (see section 4.6)

Fluorouracil should not be used in the management of non-malignant disease

4.4 Special warnings and precautions for use

It is recommended that fluorouracil be given only by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites and has the facilities for regular monitoring, of clinical, biochemical and haematological effects during and after administration.

All patients should be admitted to hospital for initial treatment.

Fluorouracil has a narrow margin of safety and is a highly toxic drug. If the following adverse effects occur, discontinuation of the therapy should be considered: leukopenia, thrombocytopenia, stomatitis, intractable vomiting, diarrhea, melena, gastrointestinal ulceration and bleeding, or hemorrhage from any site.

Haematological effects
Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C.) count commonly being observed between the 7th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day. Daily monitoring of platelet and W.B.C. count is recommended and treatment should be stopped if platelets fall below 100,000 per mm^3 or the W.B.C. count falls below 3,500 per mm^3. If the total count is less than 2000 per mm^3, and especially if there is granulocytopenia, it is recommended that the patient be placed in protective isolation in the hospital and treated with appropriate measures to prevent systemic infection.

Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to, leukopenia, granulocytopenia, pancytopenia and thrombocytopenia).

Clinical consequences of severe myelosuppresion include infections. Viral, bacterial, fungal and/or parasitic infections, either localized or systemic, may be associated with the use of fluorouracil alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal.

Gastrointestinal effects

Treatment should also be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the G.I. tract or haemorrage at any site. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken, therefore, in the selection of patients and adjustment of dosage. Treatment should be stopped in case of severe toxicity.

Loss of appetite, nausea and vomiting are common adverse effects, which generally occur during the first week of therapy. These adverse effects can often be alleviated by antiemetics, and generally subside within 2 to 3 days.

Radiotherapy

Fluorouracil treatment may potentiate necrosis caused by radiation.

Special risk patients

Fluorouracil should be used with extreme caution in patients who have previously received high-dose pelvic irradiation or alkylating agents, and in those who have a widespread involvement of bone marrow by metastatic tumors.
Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin (see section 4.5).

Particular care should be taken in the treatment of elderly or debilitated patients, as these patients may be at increased risk of severe toxicity.

Renal and hepatic impairment

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice.

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, arrhythmias, myocarditis, cardiogenic shock, sudden death, stress cardiomyopathy (takotsubo syndrome) and electrocardiographic changes (including very rare cases of QT prolongation). These adverse events are more common in patients receiving continuous infusion of 5-fluorouracil rather than bolus injection. Prior history of coronary artery disease may be a risk factor for some cardiac adverse reactions. Care should therefore be exercised in treating patients who experienced chest pain during courses of treatment, or patients with a history of heart disease. Cardiac function should be regularly monitored during treatment with fluorouracil. In case of severe cardiotoxicity the treatment should be discontinued.

Immunosuppressant effects

Vaccination with a live vaccine should be avoided in patients receiving 5-fluorouracil due to the potential for serious or fatal infections. Contact should be avoided with people who have recently been treated with polio virus vaccine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Hand-foot syndrome

The administration of fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. Continuous-infusion fluorouracil may increase the incidence and severity of palmar-plantar erythrodysesthesia. This syndrome has been characterized as a tingling sensation of hands and feet, which may progress over the next few days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Supplementation of chemotherapy with oral pyridoxine has been reported to prevent or resolve such symptoms.

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy, posterior reversible encephalopathy syndrome [PRES]) associated with 5-fluorouracil treatment have been reported from post-marketing sources. Signs or symptoms of encephalopathy are altered mental status, confusion, disorientation, coma or ataxia. If a patient develops any of these symptoms withhold treatment and test serum ammonia levels immediately. In case of elevated serum ammonia levels initiate ammonia-lowering therapy. Hyperammonaemic encephalopathy often occurs together with lactic acidosis.

Caution is necessary when administering fluorouracil to patients with renal and/or hepatic impairment. Patients with impaired renal and/or hepatic function may have an increased risk for hyperammonaemia and hyperammonaemic encephalopathy.

Tumour Lysis Syndrome

Cases of tumour lysis syndrome associated with fluorouracil treatment have been reported from post-marketing sources. Patients at increased risk of tumour lysis syndrome (e.g. with renal impairment, hyperuricemia, high tumour burden, rapid progression) should be closely monitored. Preventive measures (e.g. hydration, correction of high uric acid levels) should be considered.

Dihydropyrimidine dehydrogenase (DPD) deficiency
Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil.There have been reports of increased fluorouracil toxicity in patients who have reduced activity/deficiency of DPD. If applicable, determination of DPD enzyme activity is indicated prior to the treatment with 5-fluoropyrimidines.

DPD activity is rate limiting in the catabolism of 5-fluorouracil (see section 5.2). Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.

DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

Complete DPD deficiency
Complete DPD deficiency is rare (0.01-0.5% of Caucasians). Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with Fluorouracil injection (see section 4.3).

Partial DPD deficiency
Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Testing for DPD deficiency
Phenotype and/or genotype testing prior to the initiation of treatment with Fluorouracil injection is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

Genotypic characterisation of DPD deficiency
Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency.

The four DPYD variants c.1905+1G>A [also known as DPYD*2A], c.1679T>G [DPYD*13], c.2846A>T and c.1236G>A/HapB3 can cause complete absence or reduction of DPD enzymatic activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity.

Certain homozygous and compound heterozygous mutations in the DPYD gene locus (e.g. combinations of the four variants with at least one allele of c.1905+1G>A or c.1679T>G) are known to cause complete or near complete absence of DPD enzymatic activity.

Patients with certain heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have increased risk of severe toxicity when treated with fluoropyrimidines.

The frequency of the heterozygous c.1905+1G>A genotype in the DPYD gene in Caucasian patients is around 1%, 1.1% for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0.07 to 0.1% for c.1679T>G.

Data on the frequency of the four DPYD variants in other populations than Caucasian is limited. At the present, the four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are considered virtually absent in populations of African (-American) or Asian origin.

Phenotypic characterisation of DPD deficiency
For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma is recommended.

Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level ≥ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.

5-Fluorouracil Therapeutic drug monitoring (TDM)
TDM of 5-fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions by reducing toxicities and improving efficacy. AUC is supposed to be between 20 and 30mg x h/L.

Photosensitivity reactions
Some patients may experience photosensitivity reactions following administration of fluorouracil, it is recommended that patients are warned to avoid prolonged exposure to sunlight (see section 4.8).

Embryo-foetal toxicity
Fluorouracil showed evidence of genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with fluorouracil. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see sections 4.6 and 5.3).

Combination of 5-fluorouracil and folinic acid
The toxicity profile of 5-fluorouracil may be enhanced or shifted by folinic acid. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. When 5-fluorouracil and folinic acid are used in combination, the fluorouracil dosage must be reduced more in cases of toxicity than when fluorouracil is used alone. Toxicities observed in patients treated with the combination are qualitatively similar to those observed in patients treated with 5-fluorouracil alone.

Gastrointestinal toxicities are observed more commonly and may be more severe or even life threatening (particularly stomatitis and diarrhoea). In severe cases, 5-fluorouracil and folinic acid must be withdrawn, and supportive intravenous therapy initiated. Patients should be instructed to consult their treating physician immediately if stomatitis (mild to moderate ulcers) and/or diarrhoea (watery stools or bowel movements) two times per day occur.

Excipient information
The 10ml vial contains 40.1 mg of sodium in each vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The 20ml vial contains 80.2 mg of sodium in each vial, equivalent to 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The 100ml vial contains 401 mg of sodium in each vial, equivalent to 20% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Brivudine and sorivudine
Brivudine, sorivudine or their chemically related analogues irreversibly inhibit DPD, resulting in a significant increase in fluorouracil exposure. This may lead to increased fluoropyrimidine-related toxicities with potentially fatal outcome. Therefore, either a different antiviral therapy may be used or there should be an interval of at least 4 weeks between the administration of brivudine, sorivudine, or the analogues and the start of fluorouracil treatment (see section 4.3). In the case of accidental administration of nucleoside analogues that inhibit DPD activity to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalization is recommended.

Cytotoxic agents
Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, folinic acid interferon alfa and allopurinol.

In patients receiving cyclophosphamide, Methotrexate and 5-fluorouracil, addition of thiazide diuretics resulted in a more pronounced decrease of the number of granulocytes when compared to patients not receiving thiazides.

In patients with breast cancer, combination therapy with cyclophosphamide, methotrexate, 5-fluorouracil and tamoxifen has been reported to increase the risk of thromboembolic events.

Serious, potentially life-threatening mucositis may occur following co-administration of vinorelbine and 5-fluorouracil/folinic acid.

In combination with other myelosuppressive substances, dosage adjustment is necessary. Concomitant or previous radiation therapy may require dosage reduction. The cardiotoxicity of anthracyclines may be increased.

Increased incidence of cerebral infarction has been reported in oropharyngeal cancer patients treated with fluorouracil and cisplatin.

Calcium folinate (Folinic acid)
Folinic acid enhances the binding of fluorouracil to thymidylate synthase. Both the efficacy and toxicity of 5-fluorouracil may be increased when 5-fluorouracil is used in combination with folinic acid (see section 4.2). Side effects may be more pronounced and severe diarrhoea may occur. Life-threatening diarrhoeas have been observed if 600 mg/m^2 of fluorouracil (i.v. bolus once weekly) is given together with folinic acid.

Phenytoin
The level of phenytoin should be regularly monitored in patients taking fluorouracil and the phenytoin dosage may need to be reduced. Toxicity associated with elevated phenytoin plasma concentrations have been reported during concomitant use of phenytoin with fluorouracil or its analogues. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by fluorouracil (see section 4.4).

Warfarin
Marked elevations of prothrombin time and INR have been reported in a few patients stabilised on Warfarin therapy following initiation of fluorouracil regimes. Adequate anticoagulant response to warfarin and other coumarin-derivative therapy should be monitored regularly in patients taking fluorouracil.

Fluorouracil should be avoided in combination with clozapine due to increased risk of agranulocytosis.

Cimetidine, metronidazole and interferon may increase the plasma level of 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil.

Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy (see section 4.2).

Hepatotoxicity (increase in alkaline phosphatases, transaminases or bilirubin) has been observed commonly in patients receiving 5-fluorouracil in combination with levamisol.

Vaccination with live vaccines should be avoided in immunocompromised patients.

Laboratory values
Fluorouracil treatment may interfere with some laboratory tests. Increases in total serum thyroxine concentration (due to increased binding to globulin) have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
Fluorouracil may cause foetal harm when administered to pregnant women. There is only limited data available on the teratogenetic effects of fluorouracil in humans. However, based on the teratogenic effects detected in animal studies (in which the doses used were 1 to 3 times higher than the maximum recommended dose for humans), fluorouracil can be considered an agent that can cause foetal malformations (see section 5.3).

There are no adequate and well-controlled studies in pregnant women, however, foetal defects and miscarriages have been reported.

Women of childbearing potential should be advised to avoid becoming pregnant and use a highly effective method of contraception during treatment with fluorouracil and for at least 6 months afterwards. If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be fully informed of the potential hazard to the foetus and genetic counselling is recommended if appropriate and available. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Successful pregnancies have been reported in patients who have received chemotherapy during the second and third trimesters.

Fertility
Effects of fluorouracil on the gonads and reproduction capacity of humans are not fully known. However, studies in animals indicate impaired male and female fertility (see section 5.3). Also, drugs which inhibit DNA, RNA, and protein synthesis (such as fluorouracil), presumably interfere with gametogenesis.

Men treated with fluorouracil are advised not to father a child during and for up to 3 months following cessation of treatment. Advice on fertility preservation should be sought prior to treatment by both male and female patients because of the possibility of irreversible infertility due to therapy with fluorouracil.

Breast-feeding
Since it is not known whether Fluorouracil passes into breast milk, breast-feeding must be discontinued if the mother is treated with fluorouracil (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machinery have been performed.

Fluorouracil may induce side effects such as nausea and vomiting. It can also produce adverse events on the nervous system and visual changes which could interfere with driving or the use of heavy machinery.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with Fluorouracil Injection with the following frequencies
very common (≥1/10),
common (≥ 1.100 to <1/10),
Uncommon (≥ 1/1,00 to <1/100),
Rare (≥ 1/10,000 to < 1/1,00),
Very rare (<1/10,000),
Frequency not known (cannot be estimated from the available data).

Infections and infestations:		
Very common		Infections, Pharyngitis
Common		Sepsis
Frequency not known		Septic shock, Neutropenic sepsis, Pneumonia, Superinfection, Urinary tract infection, Device related infection, Cellulitis
Blood and lymphatic system disorders:		
Very common		Myelosuppression[a], Neutropenia, Thrombocytopenia, Leukopenia, Agranulocytosis, Anaemia and Pancytopenia
Common		Febrile neutropenia
Frequency not known		Granulocytopenia
Immune system disorders:		
Very common		Bronchospasm, Immunosuppression with an increased risk of infection
Rare		Generalized allergic reactions, Anaphylaxis, Anaphylactic shock
Frequency not known		Hypersensitivity
Endocrine disorders:		

Rare		Increase of T4 (total thyroxine). increase of T3 (total triiodothyronine)
Metabolism and nutrition disorders:		
Very common		Hyperuricemia
Uncommon		Dehydration
Frequency not known		Decreased appetite, lactic acidosis, tumour lysis syndrome
Psychiatric disorders:		
Uncommon		Euphoric mood
Rare		Confusional state
Frequency not known		Disorientation
Nervous system disorders:		
Uncommon		Nystagmus, Headache, Dizziness, Symptoms of Parkinson's disease, Pyramidal signs, Somnolence
Very rare		Leukoencephalopathy
Frequency not known		Peripheral neuropathy, Epilepsy, Hyperammonaemic encephalopathy, Cerebellar syndrome, Posterior reversible encephalopathy syndrome (PRES)
Eye disorders:		
Uncommon		Excessive lacrimation, Blurred vision, Eye movement disturbance, Optic neuritis, Diplopia, Decrease in visual acuity, Photophobia, Conjunctivitis, Blepharitis, Ectropion, Dacryostenosis
Cardiac disorders:		
Very common		Ischemic ECG abnormalities
Common		Myocardial infarction, Angina pectoris-like chest pain
Uncommon		Arrhythmia, Myocardial ischemia, Myocarditis, Cardiac insufficiency, Dilated cardiomyopathy, Cardiac shock
Very rare		Cardiac arrest, Sudden cardiac death[b]
Frequency not known		Stress cardiomyopathy (takotsubo syndrome), Intracardiac thrombus, Cardiac failure, Pericarditis
Vascular disorders:		
Rare		Cerebral, Intestinal and peripheral ischemia, Raynaud's syndrome, Thromboembolism, Thrombophlebitis/ Vein tracking
Uncommon		Hypotension
Frequency not known		Haemorrhage
Gastrointestinal disorders:		
Very common		Mucositis (Stomatitis, Oesophagitis, Proctitis), Anorexia, Watery diarrhoea, Nausea, Vomiting
Uncommon		Gastrointestinal ulceration and bleeding, Sloughing
Frequency not known		Melaena, Pneumatosis intestinalis
Hepatobiliary disorders:		
Very common		Hepatocellular injury
Very rare		Liver necrosis (cases with fatal outcome), Biliary sclerosis, Cholecystitis
Skin and subcutaneous tissue disorders:		
Very common		Alopecia. Palmar-plantar erythrodysaesthesia syndrome (Hand-foot syndrome)[c]
Uncommon		Dermatitis, Skin alterations (e.g. Dry skin, Fissure erosion, Erythema, Pruritic maculopapular rash), Exanthema, Urticaria, Photosensitivity, Hyperpigmentation of the skin, Streaky hyperpigmentation or depigmentation near the veins. Changes in the nails (e.g. Diffuse superficial blue pigmentation, Hyperpigmentation, Nail dystrophy, Pain and thickening of the nail bed, Paronychia) and Onycholysis
Frequency not known		Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders:		
Frequency not known		Drug-induced lupus erythematosus

Reproductive system and breast disorder:		
Uncommon		Spermatogenesis and Ovulation disorder
General disorders and administration site conditions:		
Very Common		Delayed wound healing, Epistaxis, Fatigue, General weakness, Tiredness, Lack of energy
Frequency not known		Pyrexia, Chest pain, Injection site reaction
Investigations:		
Common		Electrocardiogram change

[a] Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days.

[b] Cardiotoxic adverse events mostly occur during or within hours following the first treatment cycle. There is an increased risk of cardiotoxicity in patients with previous coronary heart disease or cardiomyopathy.

[c] hand-foot syndrome has been noted with protracted and high dose continuous infusion.
The syndrome begins with dysaesthesia of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

The possibility of overdosage with fluorouracil is unlikely in view of the mode of administration. High dosages or prolonged treatment with fluorouracil can result in life-threatening intoxication symptoms such as; nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia, agranulocytosis).

Uridine triacetate is a specific antidote for the treatment of 5-fluorouracil overdose or the treatment of severe early-onset toxicities. It should be administered within 96 hours after end of 5-fluorouracil infusion. In the event uridine triacetate is not available, treatment is symptomatic and supportive.

Patients who have been exposed to an overdose of fluorouracil should be monitored haematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilised

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil can also be incorporated into RNA, resulting in formation of defective RNA.

5.2 Pharmacokinetic properties

Absorption
Following rapid intravenous administration (10 - 15 mg/kg) peak plasma levels (24 - 125 microg/mL) are reached within a couple of minutes.

Distribution
After intravenous administration, Fluorouracil is distributed through the body water and disappears from the blood within 3 hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil readily enters the Cerebrospinal Fluid (C.S.F.) and brain tissue.

Biotransformation
5-fluorouracil is catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β- alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of 5-fluorouracil (see sections 4.3 and 4.4). The main part of fluorouracil is rapidly metabolized in the liver into biologically inactive metabolites, which are further converted to carbon dioxide and eliminated via the lungs.

Elimination
Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependant. Following a single IV dose of Fluorouracil approximately 15% of the dose is excreted unchanged in the urine within 6 hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

Special populations
In patients with hepatic or renal failure, biotransformation and/or elimination of fluorouracil is reduced, requiring a reduction in dose rate (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Adverse effects of fluorouracil have been reported in repeat-dose studies in rats, cats, and dogs. The main organs of toxicity in rats were the gastrointestinal tract, haemolymphopoietic system, liver, kidneys, and testes. Cardiotoxicity was observed in rats and neurotoxicity in cats and dogs.

Fluorouracil was genotoxic in the majority of the *in vitro* or *in vivo* studies performed.

Nonclinical data are inconclusive with respect to carcinogenicity. Nevertheless, the risk of carcinogenicity cannot be totally excluded.

Findings in repeat-dose toxicity studies indicate that fluorouracil has the potential to impact reproductive function and fertility in male rats. Fluorouracil was toxic to male reproductive organs, causing changes in spermatogonia chromosomal organization, inhibition of spermatogonial differentiation and transient infertility in male rats. Administration of ≥ 25 mg/kg (0.33x a human dose of 12 mg/kg, based on body surface area) weekly for 3 weeks to female rats resulted in reduced female fertility, preimplantation loss, and increased chromosomal anomalies in embryos.

Fluorouracil was foetotoxic and teratogenic in mice, rats, and hamsters. Foetal malformations included cleft palate, skeletal defects, and deformed appendages and tails. Potential effects of fluorouracil on peri and postnatal development have not been studied in animals. However, in rats fluorouracil has been found to cross the placental barrier and to cause foetal mortality.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide
Water for Injections

6.2 Incompatibilities

Fluorouracil is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, other anthracyclines and possibly methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

6.3 Shelf life

Unopened: 2 years.

Chemical and physical in-use stability has been demonstrated for 5 days at 20 - 21°C, when diluted with 0.9% Sodium Chloride Injection and 5% Glucose Injection.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Keep the vials in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Fluorouracil 25mg/ml Injection is presented in Type I conventional clear glass vials with rubber stoppers and Type I clear ONCO-TAIN vials with rubber stoppers.

Fluorouracil 25mg/ml Injection is available in the following pack sizes: 10ml, 20ml and 100ml and in packs of 1, 5 and 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pH of Fluorouracil Injection is 8.9 and the drug has maximal stability over the pH range 8.6 to 9.0.

If a precipitate has formed as a result of exposure to low temperatures, redissolve by heating to 60°C accompanied by vigorous shaking. Allow to cool to body temperature prior to use.

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

Cytotoxic Handling Guidelines

Fluorouracil should be administered only by or under the supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic drugs.

Administration
For instructions on administration, see Section 4.2.

Preparation (guidelines):

(a)	Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.
(b)	Operations such as the reconstitution of powder and transfer to syringes should be carried out only in the designated area.
(c)	The personnel carrying out these procedures should be adequately protected with special clothing, two pairs of gloves, one latex, one PVC, (the latex being worn beneath the PVC), this covers differences in permeabilities to the various antineoplastics, and eye shields. Luerlock syringes and fittings should always be used both in the preparation of cytotoxic products and for their administration.
(d)	Pregnant personnel are advised not to handle chemotherapeutic agents.
(e)	Refer to local cytotoxic guidelines before commencing.

Contamination

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. Hydrocortisone cream 1% may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with an absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

First Aid

Eye contact: Irrigate immediately with water and seek medical advice.
Skin contact: Wash thoroughly with soap and water and remove contaminated clothing.
Inhalation, Ingestion: Seek medical advice.

Disposal

Syringes, containers, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container, marked as cytotoxic waste and incinerated at a minimum of 700^{o}C. Chemical inactivation can be achieved by 5% Sodium Hypochlorite over 24 hours.

Instructions for Use

Diluents

Fluorouracil Injection B.P. may be diluted with Glucose 5% or Sodium Chloride 0.9% Injection B.P. or Water for Injections B.P. immediately before parenteral use. The remainder of solutions should be discarded after use: do not make up into multidose preparations.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

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