Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg of fluorouracil (as sodium salt formed *in situ*).

Each 5 ml vial contains 250 mg of fluorouracil.
Each 10 ml vial contains 500 mg of fluorouracil.
Each 20 ml vial contains 1000 mg of fluorouracil.
Each 50 ml vial contains 2500 mg of fluorouracil.
Each 100 ml vial contains 5000 mg of fluorouracil.

Excipients with known effect:
8.25 mg/ml (0.360 mmol/ml) sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

A clear colourless to slight yellow solution with a pH in the range of 8.6 to 9.4.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil is indicated in adults.

Fluorouracil is indicated in the treatment of the following malignancies and disease settings:

- in the treatment of metastatic colorectal cancer
- as adjuvant treatment in colon and rectal cancer
- in the treatment of advanced gastric cancer,
- in the treatment of advanced pancreatic cancer,
- in the treatment of advanced oesophageal cancer,
- in the treatment of advanced or metastatic breast cancer,
- as adjuvant treatment in patients with operable primary invasive breast cancer,
- in the treatment of inoperable locally advanced squamous cell carcinoma of the head and neck in previously untreated patients
- in the treatment of locally recurrent or metastatic squamous cell carcinoma of the head and neck

4.2 Posology and method of administration

Posology
5-fluorouracil should be administered only under the supervision of a qualified physician with extensive experience in cytotoxic treatment.

Patients must be carefully and frequently monitored during the treatment. The risks and benefits to individual patients should be carefully considered before each treatment.

Method of administration
5-fluorouracil can be administered by intravenous injection as bolus, infusion or continuous infusion for up to several days.

These are general advices. Please refer to a local or international guideline for a more (up to date) recommendation.

Precautions to be taken before handling or administering the medicinal product and
For instructions on dilution of the medicinal product before administration, see section 6.6

Intravenous administration:
The dose of 5-fluorouracil and the treatment schedule depends on the chosen treatment regimen, the indication, the general status and previous treatment of the patient. Treatment regimens vary in the combination of 5-fluorouracil with other cytotoxic agents or dose of concomitantly used folinic acid.

The number of cycles used should be decided by the treating clinician depending on local treatment protocols and guidelines; taking into consideration treatment success and tolerability in individual patients.

Initial treatment should be given in hospital.

Reduction of the dose is advisable in patients with any of the following:
1. Cachexia
2. Major surgery within preceding 30 days
3. Reduced bone marrow function
4. Impaired hepatic or renal function

Adults and elderly patients receiving 5-fluorouracil should be monitored prior to each dose for haematological (platelet, leucocyte, and granulocyte counts), gastrointestinal (stomatitis, diarrhoea, bleeding from the gastrointestinal tract), and neurological toxicity, and, if necessary, the dose of 5-fluorouracil may be either reduced or withheld.

Necessity of dosage adjustment or discontinuation of the medicinal product depends on the occurrence of undesirable effects. Haematological toxicities such as reduced leukocytes (≤ 3500/mm^3) and/or platelet counts (≤ 100000/mm^3) can require treatment interruption. Resumption of treatment must be decided by the treating clinician depending upon the clinical scenario.

Colorectal cancer:
5-fluorouracil is used in the treatment of colon and rectal cancers in a number of treatment regimens. 5-fluorouracil is preferably used along with folinic acid. Commonly used treatment regimens also combine 5-fluorouracil and folinic acid with other chemotherapeutic agents such as Irinotecan (FOLFIRI and FLIRI), Oxaliplatin (FOLFOX) or both Irinotecan and Oxaliplatin (FOLFIRINOX).

The commonly used dose range of 5-fluorouracil varies from 200-600mg/m^2 of body surface. The dose also varies depending on administration as intravenous bolus or as continuous intravenous infusion.

The dose schedules also vary depending on the chemotherapy regimen, and 5-fluorouracil dose could be repeated weekly, bimonthly or monthly.

The number of cycles varies with the treatment regimens used and also depends on the clinical decision based on treatment success and tolerability.

Breast cancer:
5-fluorouracil is commonly used in chemotherapy regimens in combination with cyclophosphamide and methotrexate (CMF), or epirubicin, cyclophosphamide (FEC) or methotrexate and leucovorin (MFL). The usual dose range is 500- 600 mg/m^2 body surface as an intravenous bolus and repeated every 3–4 weeks as necessary. In adjuvant treatment of primary invasive breast cancer, duration of treatment will usually continue for 6 cycles.

Gastric cancer and cancer of gastroesophageal junction:
Peri-operative chemotherapy with ECF regimen (epirubicin, cisplatin, 5-fluorouracil) is currently recommended. The recommended dose of 5-fluorouracil is 200 mg/m^2 body surface per day given as continuous intravenous infusion for 3 weeks. 6 cycles are recommended but this depends on treatment success and tolerability of medicinal product by the patient.

Oesophageal cancer:

5-fluorouracil is commonly used in combination with cisplatin; or cisplatin and epirubicin; or epirubicin and oxaliplatin. Dose varies between 200- 1000 mg/m^2 body surface per day as continuous intravenous infusion over several days and repeated cyclically depending upon regimen.

For cancers involving lower part of oesophagus, peri-operative chemotherapy with ECF regimen (epirubicin, cisplatin, 5-fluorouracil) is commonly recommended. The recommended dose of 5-fluorouracil is 200 mg/m^2 body surface per day given as continuous intravenous infusion for 3 weeks and repeated cyclically.
Concerning administration of 5-fluorouracil/cisplatin in combination with radiotherapy, please refer to the literature.

Pancreatic cancer:
5-fluorouracil is preferably used in combination with folinic acid or gemcitabine. Dose varies between 200- 500 mg/m^2 body surface per day as intravenous bolus injection or intravenous infusion, depending on the regimen and repeated cyclically.

Head and neck cancer:
5-fluorouracil is preferably used in combination with cisplatin or carboplatin. Dose varies between 600- 1200 mg/m^2 body surface per day as continuous intravenous infusion over several days and repeated cyclically depending upon regimen.

Concerning administration of 5-fluorouracil/ cisplatin or carboplatin in combination with radiotherapy, please refer to the literature.

Special populations
Renal or hepatic impairment
Caution is advised and the dose might need to be reduced in patients with renal or hepatic impairment.

Paediatric population
Fluorouracil is not recommended for use in children due to insufficient data on safety and efficacy.

Elderly
No dose adjustments in elderly are recommended but care should be taken to consider any concomitant condition in determining the dose.

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
- Are suffering from bone marrow depression after radiotherapy or treatment with other antineoplastic agents
- Management of non-malignant disease
- Have serious liver impairment
- 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 section 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 women (see section 4.6)

- Have known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4)

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.
Haematological effects
Fluorouracil may produce myelosuppression (including, but not limited to, leukopenia, granulocytopenia, pancytopenia and thrombocytopenia).

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.
Clinical consequences of severe myelosuppresion include infections. 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 haemorrhage 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.
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. Fluorouracil treatment may potentiate necrosis caused by radiation.
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. Interruption of therapy is followed by gradual resolution over 5 to 7 days.
Encephalopathy
Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathyposterior reversible encephalopathy syndrome [PRES], Wernicke's encephalopathy) 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 and vitamin B1 levels immediately. In case of elevated serum ammonia levels or vitamin B1 deficiency initiate 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:
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.

Impaired kidney function can lead to increased blood uracil levels resulting in an increased risk for misdiagnosis in patients with DPD deficiency with moderate or severe renal impairment.

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. Blood uracil levels should be interpreted with caution in patients with impaired kidney function (see 'Testing for DPD deficiency' above).

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).
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.

Sodium
Fluorouracil injection BP contains 7.78 mmol (178.2 mg) of sodium per maximum daily dose (600 mg/m^2). This should be taken into consideration by patients on a controlled sodium diet.

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 anti-tumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, folinic acid, interferon alfa and allopurinol.

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. 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.

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.

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

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

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 or CYP2C19 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.

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).

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.

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

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.

Vaccination with live vaccines should be avoided in immunocompromised patients.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
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 fetus and genetic counselling is recommended if appropriate and available.

Pregnancy
Fluorouracil may cause foetal harm when administered to pregnant women. There are no adequate and well-controlled studies in pregnant women, however, fetal defects and miscarriages have been reported. Based on the teratogenic effects detected in animal studies, fluorouracil can be considered an agent that can cause foetal malformations (see section 5.3). 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.

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).
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.

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 usage 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 (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
Not known (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders:	
Very common	Myelosuppression, Neutropenia,

	Thrombocytopenia, Leukopenia, Agranulocytosis, Anaemia Pancytopenia
Common	Febrile neutropenia
Not known	Granulocytopenia
Immune system disorders:	
Very common	Bronchospasm, Immunosuppression
Rare	Hypersensitivity Anaphylactic reaction Anaphylactic shock
Infections and infestations:	
Very common	Infections, Pharyngitis
Common	Sepsis
Not known	Septic shock, Neutropenic sepsis, Pneumonia, Urinary tract infection, Cellulitis
Investigations	
Common	Electrocardiogram change
Endocrine disorders:	
Rare	Thyroxine increased Tri-iodothyronine increased
Metabolism and nutrition disorders:	
Very common	Hyperuricemia
Uncommon	Dehydration
Not known	Decreased appetite, lactic acidosis, tumour lysis syndrome, Hypertriglyceridaemia, Vitamin B1 deficiency
Psychiatric disorders:	
Uncommon	Euphoric mood
Rare	Confusional state
Very rare	Disorientation
Nervous system disorders:	
Uncommon	Nystagmus, Headache, Dizziness, Symptoms of Parkinson's disease, Pyramidal signs, Somnolence
Very rare	Leukoencephalopathy Cerebellar syndrome Dysarthria Myasthenia Aphasia Convulsion Coma
Not known	Peripheral neuropathy, Epilepsy, Hyperammonaemic encephalopathy, Posterior reversible encephalopathy syndrome (PRES), Wernicke's encephalopathy
Renal and urinary disorders	
Rare	Renal failure
Eye disorders:	
Uncommon	Lacrimation increased Blurred vision, Eye movement disturbance, Optic neuritis, Diplopia,

	Decrease in visual acuity, Photophobia, Conjunctivitis, Blepharitis, Ectropion, Dacryostenosis
Cardiac disorders:	
Very common	ECG signs of myocardial ischaemia
Common	Myocardial infarction, Angina pectoris
Uncommon	Arrhythmia, Myocardial ischaemia, Myocarditis, Cardiac failure, Congestive cardiomyopathy, Cardiac shock
Very rare	Cardiac arrest, Sudden cardiac death
Not known	Intracardiac thrombus, Pericarditis, Stress cardiomyopathy (takotsubo syndrome)
Vascular disorders:	
Uncommon	Hypotension
Rare	Cerebral ischaemia, Intestinal ischaemia, Peripheral ischaemia, Raynaud's syndrome, Thromboembolism, Thrombophlebitis
Not known	Haemorrhage
Gastrointestinal disorders:	
Very common	Mucosal inflammation, stomatitis, Oesophagitis, Proctitis, Anorexia, Diarrhoea, Nausea, Vomiting
Uncommon	Gastrointestinal ulcer Gastrointestinal haemorrhage Gastrointestinal mucosal exfoliation
Not known	Melaena, Pneumatosis intestinalis, Enterocolitis, Colitis (including necrotising colitis)
Hepatobiliary disorders:	
Uncommon	Hepatocellular injury
Very rare	Hepatic necrosis, Biliary sclerosis, Cholecystitis
Skin and subcutaneous tissue disorders:	
Very common	Alopecia, Palmar-plantar erythrodysaesthesia syndrome (Hand-foot syndrome)
Uncommon	Dermatitis Dry skin Fissure erosion Erythema Pruritic maculopapular rash Exanthema Urticaria Photosensitivity Hyperpigmentation of the skin Hyperpigmentation or depigmentation near the veins Nail pigmentation

	Nail dystrophy Nail bed disorder Paronychia Onycholysis
Not known	Cutaneous lupus erythematosus
Reproductive system disorders:	
Uncommon	Azoospermia, Ovulation disorder
General disorders and administration site conditions:	
Very Common	Delayed wound healing, Epistaxis, Malaise Asthenia Fatigue
Not known	Pyrexia, Chest pain, Injection site discolouration, Local reaction caused by extravasation (pain, swelling, erythema)

Description of selected adverse reactions

Myelosuppression
Observed onset of myelosuppression varied between 7-10 days, nadir between 9-14 days, and recovery occurred between 21-28 days.

Cardiac disorders
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 (see section 4.4).

Hepatobiliary disorders
Fatal cases of hepatic necrosis have been reported.

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

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).

Treatment consists of drug discontinuation and supportive measures (see section 4.4).
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

Pharmacotherapeutic group: Antineoplastic agents; Antimetabolites; Pyrimidine analogues
ATC code: L01BC02.

Mechanism of action
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, interfering with RNA synthesis.

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 pharmacologically inactive metabolites.

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 which might require dose reduction (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. 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. 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 (For pH adjustment)

Hydrochloric acid (For pH adjustment)
Water for Injections

6.2 Incompatibilities

Fluorouracil is incompatible with Folinic Acid, Carboplatin, Cisplatin, Cytarabine, Diazepam, Doxorubicin, Droperidol, Filgrastim, Gallium nitrate, Methotrexate, Metoclopramide, Morphine, Ondansetron, parenteral nutrition, Vinorelbine, other Anthracyclines.

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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Shelf life of unopened vial:
2 years.

Vial after first opening:
Use immediately after opening

Shelf Life after dilution
In use: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with Glucose 5% or Sodium Chloride 0.9% Injection or Water for Injections at concentration 0.98 mg/ml of Fluorouracil.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

Keep vial in the outer carton in order to protect from light.

The pH of Fluorouracil Injection is 8.9 and the drug has maximal stability over the pH range 8.6 to 9.4

For storage condition of the diluted medicinal product, see section 6.3.

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.

The product should be discarded if it appears brown or dark yellow in solution.

6.5 Nature and contents of container

Fluorouracil Injection 50 mg/ml, 20 ml is filled in 20 ml Type I clear glass vials with rubber closure.
Fluorouracil Injection 50 mg/ml, 5 ml is filled in 5 ml Type I clear glass vials with rubber closure.
Fluorouracil Injection 50 mg/ml, 10 ml is filled in 10 ml Type I clear glass vials with rubber closure.
Fluorouracil Injection 50 mg/ml, 50 ml is filled in 50 ml Type I clear glass vials with rubber closure.
Fluorouracil Injection 50 mg/ml, 100ml is filled in 100 ml Type I clear glass vials with rubber closure.

Pack sizes:
Pack of 1 x 5 ml vial
Pack of 1 x 10 ml vial
Pack of 1 x 20 ml vial
Pack of 1 x 50ml vial
Pack of 1 x 100 ml vial
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

Fluorouracil Injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

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.

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

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.

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.

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 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 guidelines before commencing.

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°C.

Chemical inactivation can be achieved by 5% sodium Hypochlorite over 24 hours.

Instruction for Use

Diluents

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with Glucose 5% or Sodium Chloride 0.9% Injection or Water for Injections at concentration 0.98 mg/ml of fluorouracil.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The product should be discarded if it appears brown or dark yellow in solution.

The remainder of solutions should be discarded after use: do not make up into multidose preparations.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/091/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th February 2010
Date of last renewal: 28th April 2014

10 DATE OF REVISION OF THE TEXT

March 2025