SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50 mg/ml Solution for injection/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 100 ml vial contains 5000 mg of fluorouracil.

Excipient(s) with known effect: 6.3 mg/ml (0.27 mmol/ml) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless to almost colourless solution with a pH in the range of 8.5 – 9.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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.

Posology

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 ($\leq 3500/mm^3$) and/or platelet counts ($\leq 100000/mm^3$) 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 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.

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

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 dosage adjustment necessary.

Method of administration
5-fluorouracil can be administered by intravenous injection as bolus, infusion or continuous infusion for up to several days or by intra-arterial infusion.
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For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the fluorouracil or to any of the excipients listed in section 6.1.
- Serious infections (e.g. *Herpes zoster*, chickenpox).
- Seriously debilitated patients.
- Bone marrow depression after radiotherapy or treatment with other antineoplastic agents.
- Management of non-malignant disease.
- Serious liver impairment.
- Recent or concomitant treatment with brivudine. Brivudin is a potent inhibitor of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD) (see section 4.4 and 4.5 for drug-drug interaction).
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4).
- Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

4.4 Special warnings and precautions for use

It is recommended that fluorouracil should only be given 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.

Adequate treatment with fluorouracil is usually followed by leukopenia, the lowest white blood cell (W.B.C.) count commonly being observed between the 7^{th} and 14^{th} day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30^{th} 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.

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.

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of fluorouracil. Care should therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

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.

<u>Complete DPD deficiency</u>
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 (see section 4.3).

<u>Partial DPD deficiency</u>
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 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 $\geq$ 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 $\geq$ 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.

Brivudine must not be administered concomitantly with 5-fluorouracil. Fatal cases have been reported following this drug interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of 5-fluorouracil therapy. Treatment with brivudine can be started 24 hours after the last dose of 5-fluorouracil. (see section 4.3 and 4.5)
In the event of accidental administration of brivudine to patients being treated with 5-fluorouracil, effective measures should be taken to reduce the toxicity of 5-fluorouracil. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Vaccination with a live vaccine should be avoided in patients receiving 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.

It is not advisable to prolonged exposure to sunlight because of the risk of photosensitivity.

Use with caution in patients who have had high-dose pelvic radiation.

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 leukopenia, 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.

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

Women of childbearing potential and men have to use effective contraception during and up to 6 months after treatment.

Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin.

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 5-fluorouracil. In case of severe cardiotoxicity the treatment should be discontinued.

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.

Sodium:
Fluorouracil contains 6.3 mg/ml (0.27 mmol/ml) sodium. 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: a clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil, tegafur), resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be administered concomitantly with 5-fluorouracil (see section 4.3 and 4.4). There must be at least a 4-week waiting period between end of treatment with brivudine and start of 5-fluorouracil therapy. Treatment with brivudine can be started 24 hours after the last dose of 5-fluorouracil.

Various agents have been reported to biochemically modulate the anti-tumour efficacy or toxicity of fluorouracil. Common drugs include methotrexate, metronidazole, leucovorin interferon alpha and allopurinol.

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 (IV 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.

Marked elevations of prothrombin time and INR have been reported in a few patients stabilised on warfarin therapy following initiation of fluorouracil regimes.

If applicable, determination of DPD enzyme activity is indicated prior to treatment with 5- fluoropyrimidines.

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

In patients receiving phenytoin and fluorouracil concomitantly, an increase of phenytoin plasma concentration has been reported resulting in symptoms of phenytoin toxicity.

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

Pregnancy

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

Women of childbearing potential should be advised to avoid becoming pregnant and use an effective method of contraception during treatment with fluorouracil and up to 6 months afterwards (see section 4.4). 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.

Breastfeeding

Since it is not known whether fluorouracil passes into breast milk, breast-feeding must be discontinued if the mother is treated with fluorouracil.

Fertility

Men treated with fluorouracil are advised not to father a child during and for up to 6 months following cessation of treatment (see section 4.4). Advice on conservation of sperm should be sought prior to treatment 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 event on nervous system and visual changes which could interfere driving or the usage of heavy machinery.

4.8 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction).
Adverse reactions according to MedDRA system organ class and in decreasing frequency are listed below. Frequencies are defined using the following convention:

Very common (≥1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1000 to < 1/100),
Rare (≥ 1/10000 to < 1/1000),
Very rare (< 1/10000),
Not known (cannot be estimated from the available data).

	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 (cannot be estimated from the available data)**
Infections and infestations	Infections					
Blood and lymphatic system disorders	Myelosuppression [(1)], neutropenia, thrombocytopenia, leucopenia, agranulocytosis, anaemia and pancytopenia.	Febrile neutropenia				
Immune system disorders	Bronchospasm, immunosuppression with an increased risk of infection.			Generalized allergic reactions, anaphylaxis, anaphylactic shock.		
Endocrine disorders				Increase of T4 (total thyroxin), increase of T3 (total trijodthyronin).		

	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 (cannot be estimated from the available data)**
Metabolism and nutrition disorders	Hyperuricemia					Lactic acidosis, tumour lysis syndrome.
Psychiatric disorders				Confusion		
Nervous system disorders			Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, euphoria, somnolence.		Symptoms of leucoencephalopathy including ataxie, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma.	Peripheral neuropathy may occur, hyperammonaemic encephalopathy, posterior reversible encephalopathy syndrome (PRES).
Eye disorders			Excessive lacrimation, blurred vision, eye movement disturbance, optic neuritis, diplopia, decrease in visual acuity, photophobia, conjunctivitis, blepharitis, ectropion, dacryostenosis.			
Cardiac disorders	Ischemic ECG abnormalities.	Angina pectoris-like chest pain.	Arrhythmia, myocardial infarction, myocardial ischemia myocarditis,		Cardiac arrest, sudden cardiac death.[(2)]	Pericarditis, stress cardiomyopathy (takotsubo syndrome).

	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 (cannot be estimated from the available data)**
			heart insufficiency, dilative cardiomyopathy, cardiac shock.			
Vascular disorders			Hypotension	Cerebral, intestinal and peripheral ischemia, Raynaud's syndrome, thromboembolism, thrombophlebitis/vein tracking.		
Gastrointestinal disorders (3)	Mucositis (stomatitis, eosophagitis, pharyngitis, proctitis), anorexia, watery diarrhoea, nausea, vomiting.		Dehydration, sepsis, gastrointestinal ulceration and bleeding, sloughing.			Pneumatosis intestinalis
Hepatobiliary disorders			Liver cell damage.		Liver necrosis (cases with fatal outcome), Biliary sclerosis, Cholecystitis.	
Skin and subcutaneous tissue disorders	Alopecia. Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) (4).		Dermatitis, skin alterations (e.g. dry skin, fissure erosion, erythema, pruritic maculopapul			Cutaneous lupus erythematosus

	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 (cannot be estimated from the available data)
			ar 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 onycholyse.			
Reproductive system and breast disorder			Spermatogenesis and ovulation disorder.			
General disorders and administration site conditions	Delayed wound healing, epistaxis, fatigue, general weakness, tiredness, lack of energy.					Fever

(1) Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days.

(2) 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.
(3) Gastrointestinal adverse events are very common and may be life-threatening.
(4) Palmar-plantar erythrodysaesthesia syndrome (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: Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions but commonly are more pronounced particularly, the following adverse reactions might occur: 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: Pyrimidine analogues, ATC code: L01BC02.

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 may also interfere with RNA synthesis.

5.2 Pharmacokinetic properties

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 C.S.F. and brain tissue.

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 section 4.3 and 4.4).

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 to inactive metabolites by the usual body mechanisms for uracil. Hepatic impairment may result in slower metabolism of fluorouracil and may require dose adjustment.

5.3 Preclinical safety data

Preclinical information has not been included, as the clinical toxicity profile of fluorouracil has been established after many years of clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Fluorouracil is incompatible with folinic acid, carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, methotrexate, metoclopramide, morphine, ondansetrone, parenteral nutrition, vinorelbin, and 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:
Presentation 250 mg/5 ml – 18 months
Presentation 500 mg/10 ml – 2 years
Presentation 1000 mg/20 ml – 2 years
Presentation 5000 mg/100 ml – 2 years

Shelf Life after dilution
In use: Chemical and physical in-use stability has been demonstrated for 5 days at 20º - 25ºC and 2º - 8ºC with Water for Injection, Glucose 5% and Sodium Chloride 0.9% solutions at concentrations 0.5 mg/ml, 2.9 mg/ml and 4.0 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 and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

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

If a precipitate has formed as a result of exposure to low temperatures, re-dissolve 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 50 mg/ml is filled in type I, clear glass vials (with volumes of 5 ml, 10 ml, 20 ml and 100 ml), closed with rubber stoppers and flip-off caps.

Pack sizes: 1 vial.

6.6 Special precautions for disposal

The pH of Fluorouracil is 8.9 and the drug has maximal stability over the pH range 8.5 and 9.1.

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 instruction on administration, see section 4.2.

Preparation (guidelines):
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°C.

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

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.

Instruction for Use
Diluents
Chemical and physical in-use stability has been demonstrated for 5 days at 20º - 25ºC and 2º - 8ºC with Water for Injection, Glucose 5% and Sodium Chloride 0.9% solutions at concentrations 0.5 mg/ml, 2.0 mg/ml and 4.0 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 and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

Hikma Farmacêutica (Portugal), S.A.

Estrada do Rio da Mó, 8, 8A e 8B – Fervença

2705-906 Terrugem SNT

Portugal

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