SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil Injection 25 mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Fluorouracil Injection contains:

2500 mg fluorouracil in 100 ml solution (25 mg/ml)

Excipient with known effect: Sodium

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Fluorouracil Injection 25 mg/ml, solution for injection, is a clear, colourless or almost colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil Injection 25 mg/ml, solution for injection, may be used alone or in combination, for its palliative action in the management of common malignancies particularly cancer of the colon and breast, either as single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Routes of administration:

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

Adults:

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 0.8 – 1 gram. It is customary to calculate the dose in accordance with the patient's actual bodyweight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight is used as the basis for calculation.

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.

ADULT DOSE:

The following regimens 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 % NaCl injection and 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 three further doses. An alternative regime 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 – 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 fluorouracil 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 fluorouracil should be used.

CHILDREN:

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

ELDERLY:

Fluorouracil should be used in the elderly with similar considerations as with normal adult doses.

4.3 Contraindications

Fluorouracil is contraindicated in the following:

- hypersensitivity to fluorouracil or to any of the excipients listed in section 6.1,,
- bone marrow depression after radiotherapy or treatment with other antineoplastic agents,
- management of non-malignant disease,

- serious liver impairment,
- serious infections (e.g. Herpes zoster, chickenpox),
- seriously debilitated patients,
- breast feeding women (see section 4.6),
- known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4),
- recent or concomitant treatment with brivudine (see also sections 4.4 and 4.5 for drug interaction).

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.

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.

Haematotoxicity

Adequate treatment with fluorouracil is usually followed by leukopenia, the lowest white blood cell (WBC) 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 WBC count is recommended and treatment should be stopped if platelets fall below 100,000 per mm^3 or the WBC count falls below 3,500 per mm^3. If the total count is less than 2,000 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.

Gastrointestinal toxicity

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 GI tract or haemorrhage at any site.

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.

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy, posterior 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 appropriate 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 25 mg/ml (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 25 mg/ml 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.

Brivudine

Brivudine must not be administered concomitantly with 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 Fluorouracil therapy. Treatment with brivudine can be started 24 hours after the last dose of Fluorouracil. (see section 4.3 and 4.5)

In the event of accidental administration of brivudine to patients being treated with Fluorouracil, effective measures should be taken to reduce the toxicity of Fluorouracil. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Phenytoin

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

Renal or hepatic impairment

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

Photosensitivity

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

Pelvic radiation

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

Life vaccines

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.

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.

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

Sodium

This medicinal product contains 408.28 mg sodium per 100 ml vial, equivalent to 20.41% 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

A clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 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 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 Fluorouracil therapy. Treatment with brivudine can be started 24 hours after the last dose of Fluorouracil.

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil, common drugs include methotrexate, metronidazole, leucovorin, interferon alfa as well as allopurinol and cimetidine which can affect the availability of the active drug.

Cytotoxic medicinal products
Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy (see section 4.2). In combination with other myelosuppressive substances, dosage adjustment is necessary.

Radiation
Concomitant or previous radiation therapy may require dosage reduction.

Folinic acid
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/m² of fluorouracil (i.v. bolus once weekly) is given together with folinic acid.

Phenytoin
Where phenytoin and fluorouracil have been administered concomitantly, there have been reports of elevated plasma levels of phenytoin, resulting in symptoms of phenytoin intoxication (see 4.4).

Cimetidine, metronidazole or interferon
Cimetidine, metronidazole and interferone may increase the plasma level of 5-

fluorouracil, thereby increasing the toxicity of 5-fluorouracil.

Thiazide diuretics, cyclophosphamide and methotrexate
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.

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

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

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

Anthracyclines
The cardiotoxicity of anthracyclines may be increased.

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

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

Live vaccines
Vaccination with live vaccines should be avoided in immunocompromised patients.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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 an effective method of contraception during treatment with fluorouracil and 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. Fluorouracil should be used during

pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

Fertility
Men treated with fluorouracil are advised not to father a child during and for up to 3 months following cessation of treatment. 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

Summary of the safety profile

The most commonly reported undesirable effects are gastrointestinal complaints like diarrhoea, nausea and mucositis. Leukopenia is also very common and the precautions described above should be followed.

Frequency assessment:

Very common (≥ 1/10) Common (≥ 1/100, < 1/10) Uncommon (≥ 1/1,000, < 1/100) Rare (≥ 1/10,000, < 1/1,000)

Very rare (< 1/10,000), not known

Infections and infestations	Very common Infections Uncommon Sepsis
Blood and lymphatic system disorders	Very common Myelosuppression (Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days), neutropenia, leukopenia, granulocytopenia, thrombocytopenia, agranulocytosis, anemia, pancytopenia Common Febrile Neutropenia

Immune system disorders	Very common Immunosuppression Rare Generalized allergic reactions, anaphylactic reaction, anaphylactic shock
Endocrine disorders	Rare Increase of T4 (total thyroxin), increase of T3 (total trijodthyronin)
Metabolism and nutrition disorders	Very common Hyperuricemia Uncommon Dehydration Not known Lactic acidosis, tumour lysis syndrome, hypertriglyceridaemia, vitamin B1 deficiency
Psychiatric disorders	Uncommon Euphoria Rare Confusion Very rare Disorientation
Nervous system disorders	Uncommon Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramid signs, somnolence, opticus neuritis Rare Extrapyramidalmotoric disturbances, cerebellar disturbances, cortical disturbances, peripheral neuropathy Very rare leuko-encephalopathy including ataxia, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma Not known Hyperammonaemic encephalopathy, posterior reversible encephalopathy syndrome (PRES), Wernicke’s encephalopathy
Eye disorders	Common Conjunctivitis Uncommon Excessive lacrimation, blurred vision, eye movement disturbance, diplopia, decrease in visual acuity, photophobia, blepharitis, ectropion, dacryostenosis

Cardiac disorders	Very common Ischaemic ECG abnormalities Common Angina pectoris-like chest pain, tachycardia Uncommon Arrhythmia, myocarditis, myocardial ischaemia, cardiac failure, myocardial infarction, dilatative cardiomyopathy, cardiac shock Very rare Cardiac arrest, sudden cardiac death Not known Pericarditis, stress cardiomyopathy (takotsubo syndrome)
Vascular disorders	Uncommon Hypotension Rare Vasculitis, cerebral ischaemia, intestinal ischaemia, peripheral ischaemia, Raynaud's phenomenon, thromboembolism, thrombophlebitis/vein tracking
Respiratory, thoracic and mediastinal disorders	Very common Bronchospasm, epistaxis Uncommon Dyspnea
Gastrointestinal disorders	Very common Gastrointestinal adverse events are very common and may be life-threatening. Mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), anorexia, watery diarrhoea, nausea, vomiting Uncommon Gastrointestinal ulceration, gastrointestinal hemorrhage Not known Pneumatosis intestinalis, enterocolitis, colitis (including necrotising colitis)
Hepatobiliary disorders	Uncommon Liver cell damage 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) 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. Uncommon Dermatitis, skin alterations (e.g. dry skin, fissure erosion, erythema, pruritic maculopapular rash), exanthema, urticaria, photosensitivity, hyperpigmentation, hypopigmentation, streaky hyperpigmentation or depigmentation near the veins, nail disorders (e.g. diffuse superficial blue pigmentation, nail hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia), onycholysis, recall phenomenon Not known Cutaneous lupus erythematosus
Renal and urinary disorders	Very rare Renal failure
Reproductive system and breast disorder	Uncommon Spermatogenesis and ovulation disorder
General disorders and administration site conditions	Very common Fever, delayed wound healing, fatigue, malaise, weakness Not known Local reaction caused by extravasation (pain, swelling, erythema)

Description of selected adverse reactions

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.

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 the Yellow Card Scheme at via www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play Apple App Sore.

4.9 Overdose

Symptoms
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 and agranulocytosis).

Treatment
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

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.

Pharmacotherapeutic group:	Antimetabolite
ATC code:	L01BC02

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 CSF and brain tissue.

5-fluorouracil is catabolised by the enzyme 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. 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 by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, water for injections

6.2 Incompatibilities

Fluorouracil is incompatible with calcium folinate, carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutrition, vinorelbin, other anthracyclines.

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

6.3 Shelf life

2 years

Fluorouracil Injection 25 mg/ml, solution for injection, is intended for single use only.

The chemical and physical in-use stability of the solution diluted with glucose or sodium chloride injection has been demonstrated for 24 hours at a temperature not exceeding 25 °C.

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

Do not store Fluorouracil Injection 25 mg/ml, solution for injection, above 25 °C.

Do not refrigerate or freeze.

Keep the container in the outer carton.

If a precipitate has formed as a result of exposure to low temperatures, redissolve by heating to 40 °C accompanied by vigorous shaking. Allow to cool to body temperature prior to use.

6.5 Nature and contents of container

Type I conventional clear glass vials, rubber closures. The rubber stopper is protected by a flanged aluminium cap with a flip-off top.

2500 mg/100 ml: Pack Size: Singles, 10

6.6 Special precautions for disposal and other handling

Fluorouracil Injection 25 mg/ml, solution for injection, should only be opened by trained staff and as with all cytotoxic agents, precautions should be taken to avoid exposing staff during pregnancy. Preparation of solution for administration should be carried out in a designated handling area and working over a washable tray or disposable plastic-backed absorbent paper. Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

On completion, any exposed surface should be thoroughly cleaned and hands and face washed. Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of spillage, operators should put on gloves, face masks, 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.

Disposal:

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures (incineration).

Diluents:

Fluorouracil injection 25 mg/ml, solution for injection, may be diluted with 5 % glucose or 0.9 % sodium chloride intravenous infusions immediately before parenteral use. The remainder of solutions should be discarded after use; do not make up into multi-dose preparations.

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.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
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Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 11587/0021

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