Fluorouracil 50 mg/ml Solution for Injection or Infusion

Summary of Product Characteristics Updated 24-Apr-2019 | Accord Healthcare Limited

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 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/mm3) and/or platelet counts (≤ 100000/mm3) 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.

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.

4.3 Contraindications

Hypersensitivity to the fluorouracil or to any of the excipients listed in section 6.1.

Fluorouracil is contraindicated in the following

• 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

• Fluorouracil (5-FU) must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin und analogues are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD) (see section 4.4 and 4.5).

• Fluorouracil (5-FU) must not be given to patients homozygotic for dihydropyrimidine dehydrogenase (DPD).

• Fluorouracil is strictly contraindicated in pregnant or breast feeding women **(see section 4.6)**.

• In patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see section 4.4)

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 leucopenia, 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.

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, arrhythmias, myocarditis, cardiogenic shock, sudden death 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 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.

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.

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy) 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.

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.

Dihydropyrimidine dehydrogenase (DPD) deficiency

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of DPD activity.

Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants), which can cause complete or near complete absence of DPD enzymatic activity (as determined from laboratory assays), have the highest risk of life-threatening or fatal toxicity and should not be treated with 5-fluorouracil (see section 4.3). No dose has been proven safe for patients with complete absence of DPD activity.

Patients with certain heterozygous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have been shown to have increased risk of severe toxicity when treated with fluoropyrimidines.

The frequency of the heterozygous DPYD*2A 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. Genotyping for these alleles is recommended to identify patients at increased risk for severe toxicity. Data on the frequency of these DPYD variants in other populations than Caucasian is limited. It cannot be excluded that other rare variants may also be associated with an increased risk of severe toxicity.

Patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD gene) and where the benefits of 5-fluorouracil are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), must be treated with extreme caution and frequent monitoring with dose adjustment according to toxicity should be conducted. A reduction of the starting dose in these patients may be considered to avoid serious toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test. It has been reported that the DPYD*2A, c.1679T>G variants lead to a greater reduction in enzymatic activity compared to other variants with a higher risk of side effects. The consequences of a reduced dose on the efficacy are currently uncertain. Therefore, in the absence of serious toxicity the dose could be increased while carefully monitoring the patient.

The patients who are tested negative for the above-mentioned alleles may still have a risk of severe adverse events.

In patients with unrecognised DPD deficiency treated with 5-fluoruracil as well as in those patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur (see section 4.9). In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

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

Nucleoside analogues, e.g. brivudin and sorivudin, which affect DPD activity may cause increased plasma concentrations and increased toxicity of fluoropyrimidines (see section 4.5). Therefore, an interval of at least 4 weeks between administration of fluorouracil and brivudin, sorivudin or analogues should be kept. In the case of accidental administration of nucleoside analogues to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalisation is recommended. Any measure to prevent systemic infections and dehydration should be commenced.

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 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.

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.

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

Various agents have been reported to biochemically modulate the anti-tumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, leucovorin interferon alfa 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/m² 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.

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

The enzyme dihydropyrimidin dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil. Nucleoside analogues, e.g. brivudin and sorivudin, may induce an increase in plasma concentrations of 5-FU or other fluoropyrimidines accompanied by toxicological reactions. Therefore, a time interval of minimum 4 weeks between administration of fluorouracil and brivudin, sorivudin and analogues should be kept.

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

Cimetidine, metronidazole and interferone 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 upto 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. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

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.

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

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).

Blood and lymphatic system disorders:

Common

febrile neutropenia

Very common

Myelosuppression (Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days), neutropenia, thrombocytopenia, leucopenia, agranulocytosis, anaemia and pancytopenia.

Immune system disorders:

Very common

Bronchospasm, immunosuppression with an increased risk of infection.

Rare

Generalized allergic reactions, anaphylaxis, anaphylactic shock.

Infections and infestations

Very common

Infections

Endocrine disorders:

Rare:

Increase of T4 (total thyroxin), increase of T3 (total riiodothyronine).

Metabolism and nutrition disorders:

Very common

Hyperuricemia.

Psychiatric disorders:

Uncommon:

Euphoria.

Rare:

Reversible confusional state may occur.

Very rare:

Disorientation

Nervous system disorders:

Uncommon

Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, euphoria, somnolence

Very rare

Symptoms of leucoencephalopathy including ataxia, Acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma, kidney failure.

Not Known:

Peripheral neuropathy may occur, hyperammonaemic encephalopathy

Eye disorders:

Systemic fluorouracil treatment has been associated with various types of ocular toxicity.

Uncommon

Excessive lacrimation, blurred vision, eye movement disturbance, optic neuritis, diplopia, decrease in visual acuity, photophobia, conjunctivitis, blepharitis, ectropion, dacryostenosis

Cardiac disorders:

Very common

Ischemic ECG abnormalities.

Common

Angina pectoris-like chest pain.

Uncommon

Arrhythmia, myocardial infarction, myocardial ishchemia myocarditis, heart insufficiency, dilative cardiomyopathy, cardiac shock.

Very rare

Cardiac arrest, sudden cardiac death

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.

Not known

Tachycardia, breathlessness, pericarditis

Vascular disorders:

Rare

Cerebral, intestinal and peripheral ischemia, Raynaud's syndrome, thromboembolism, thrombophlebitis/vein tracking,

Uncommon

Hypotension

Gastrointestinal disorders:

Very common

Gastrointestinal adverse events are very common and may be life-threatening. Mucositis (stomatitis, eosophagitis, pharyngitis, proctitis), anorexia, watery diarrhoea, nausea, vomiting.

Uncommon

Dehydration, sepsis, gastrointestinal ulceration and bleeding (may result in therapy being discontinued), sloughing

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 may be seen in a substantial number of cases, particularly females, but is reversible.

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 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:

Uncommon

Spermatogenesis and ovulation disorder

General disorders and administration site conditions:

Very common

Delayed wound healing, epistaxis, malaise, weakness, fatigue.

Not Known

Fever, vein discolouration proximal to injection sites

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, 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: **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 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.

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-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).

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

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, Ondansetrone, parenteral nutrition, Vinorelbin, 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 immidiately 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, 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, 20 ml is filled in 20 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 1X 5 ml vial

Pack of 1X 10 ml vial

Pack of 1X 20 ml vial

Pack of 1X 50 ml vial

Pack of 1X 100 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 Limited,

319, Pinner Road,

North Harrow,

Middlesex, HA1 4HF,

United Kingdom

8. Marketing authorisation number(s)

PL 20075/0078

9. Date of first authorisation/renewal of the authorisation

10/06/2009 / 28/04/2014

10. Date of revision of the text

08/04/2019

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