Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Fluroxan 500 Injection

2. Qualitative and quantitative composition

Each 10 ml contains 5- Fluorouracil BP 500 mg

S1	Name of material	Specification	Quality per 10 ml	Used as
01	5- Fluorouracil	BP	500 mg	Active material
02	Tris (Hydroxymethyl) Aminomethane	BP	800 mg	Diluent
03	Sodium Hydroxide	BP	q.s. to adjust pH	Ph. Adjusting Agent
04	Water for Injection	USP	q.s. to 10 ml	Solvent

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend upon the condition of the patient, the type of carcinoma being

treated and whether Fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight should be used as the basis for the calculation.

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

Fluorouracil injection should not be mixed directly, in the same container, with other chemotherapeutic agents or intravenous additives.

Fluorouracil is often administered concomitantly with leucovorin which may potentiate the therapeutic effects of fluorouracil. Therefore, the toxicity of fluorouracil, especially GI and hematologic, may be increased. Careful monitoring should be observed and the dose of fluorouracil may be decreased based on current guidelines.

Adult Dose

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

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

Intravenous infusion: 15mg/kg bodyweight but not more than 1g per infusion, diluted in 500ml of 5% glucose or 0.9% NaCl injection and given by intravenous infusion at a rate of 40 drops per minute 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 - 15g has been reached.

Intravenous Injection: 12mg/kg bodyweight, but not more than the recommended 1g daily dose may be given daily for 3 days and then, if there is no evidence of toxicity, 6mg/kg on alternate days for 3 further doses. An alternative regimen is 15mg/kg as a single intravenous injection once a week throughout the course.

Intra-arterial Infusion: 5/7.5mg/kg 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. If toxic symptoms appear during maintenance, therapy must be discontinued until the symptoms resolve.

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

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1 g daily. A more recent alternative method is to give 15mg/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 5FU 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 5FU should be used.

Dose reduction in certain situations

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

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

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

4) Impaired hepatic or renal function

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

Children

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

Elderly

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

4.3 Contraindications

Fluorouracil is contraindicated in patients who/ with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Are seriously debilitated
- Are suffering from bone marrow depression after radiotherapy or treatment with other antineoplastic agents
- Are suffering from a potentially serious infection
- Have a poor nutritional state
- Are pregnant or breast feeding
- Have a known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
- Have been treated with brivudine, sorivudine or their chemically related analogues, which are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD), which degrades fluorouracil. Fluorouracil must not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues.

Fluorouracil should not be used in the management of nonmalignant disease.

4.4 Special warnings and precautions for use

It is recommended that Fluorouracil be given only by, or under the strict supervision of a qualified physician who is conversant with the use of potent antimetabolites.

All patients should be admitted to hospital for initial treatment.

The most pronounced and dose-limiting toxic effects of fluorouracil are on the normal, rapidly proliferating cells of the bone marrow and the lining of the gastrointestinal tract. The immunosuppressive effect of fluorouracil may cause a higher incidence of microbial infections, delayed wound healing and bleeding of the gums.

Hematological effects

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

Gastrointestinal effects

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhea or bleeding from the gastrointestinal tract of hemorrhage at any site, oesophagopharyngitis or intractable vomiting.
Fluorouracil should be resumed only when the patient has recovered from the above signs. 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.

Radiotherapy

Fluorouracil treatment may potentiate necrosis caused by radiation.

Special risk patients

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

Fluorouracil should be used with extreme caution in poor risk patients who have recently undergone surgery, have a history of high-dose irradiation of bone marrow-bearing areas (pelvis, spine, ribs, etc.) or prior use of another chemotherapeutic agent causing myelosuppression, have a widespread involvement of bone marrow by metastatic tumours, or those with reduced renal or liver function, jaundice or who have a poor nutritional state. Severe toxicity and fatalities are more likely in poor risk patients, but have occasionally occurred in patients who are in relatively good condition. Any form of therapy which adds to the stress of the patient, interferes with nutritional uptake or depresses the bone marrow function, will increase the toxicity of fluorouracil. If therapy is continued careful monitoring of the patient is required.

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 5fluorouracil 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.

Careful consideration should be given to re-administration of Fluorouracil after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death. Cardiac function should be regularly monitored during treatment with fluorouracil. In case of severe cardiotoxicity, the treatment should be discontinued.

Immunosuppressant effects/Increased susceptibility to infections

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

Patients with leukemia who are in remission should not receive vaccines containing weakened viruses until three months has elapsed since their last chemotherapy session. Furthermore, immunization with orally administered vaccines containing the poliomyelitis virus must be postponed for those persons coming into direct contact with the patient, particularly family members.

Hand-foot syndrome

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

Encephalopathy

Cases of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy) 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

DPD activity is rate limiting in the catabolism of 5-fluorouracil. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity, including for example stomatitis, diarrhea, 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.

Partial DPD deficiency

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

Testing for DPD deficiency

Phenotype and/or genotype testing prior to the initiation of treatment with Fluorouracil injection is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines. Impaired kidney function can lead to increased blood uracil levels resulting in an increased risk for misdiagnosis in patients with DPD deficiency with moderate or severe renal impairment.

Genotypic characterization of DPD deficiency

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

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

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

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

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

Phenotypic characterisation of DPD deficiency

For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma is recommended.
Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity.
A blood uracil level ≥ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.

5-Fluorouracil Therapeutic drug monitoring (TDM)

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

Nucleoside analogues, e.g. Brivudine and sorivudine, which affect DPD activity may cause increased plasma concentrations and increased toxicity of fluoropyrimidines. Therefore, an interval of at least 4 weeks between administration of fluorouracil and brivudine, sorivudine 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 hospitalization is recommended. Any measure to prevent systemic infections and dehydration should be commenced.

Photosensitivity reactions

Some patients may experience photosensitivity reactions following administration of fluorouracil, it is recommended that patients are warned to avoid prolonged exposure to sunlight.

Sodium content

Fluorouracil 250 mg/5 ml contains 40.1 mg of sodium in each vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Fluorouracil 500 mg/10 ml contains 80.2 mg of sodium in each vial, equivalent to 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Fluorouracil 1 g/20 ml contains 160.4 mg of sodium in each vial, equivalent to 8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Fluorouracil 2.5 g/50 ml contains 401 mg of sodium in each vial, equivalent to 20% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Fluorouracil 5 g/100 ml contains 802 mg of sodium in each vial, equivalent to 40% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product may be further prepared for administration with sodium-containing solutions and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

Various purines, pyrimidines, and antimetabolites have shown biochemical modulation of fluorouracil in in vitro test systems. Purines include inosine, guanosine, guanosine-5'-phosphate and deoxyinosine. Pyrimidines include thymidine, uridine and cytidine. Antimetabolites include methotrexate, tamoxifen, interferon, phosphonoacteyl-L-aspartate (PALA), allopurinol, hydroxyurea, dipyridamol and leucovorin (folinic acid). Synergistic cytotoxic interactions, such as those involving fluorouracil with leucovorin, have shown beneficial therapeutic effects, particularly in colon cancer. However, the drug combination may result in increased clinical toxicity (gastrointestinal side effects) of the fluorouracil

component. Other drugs include metronidazole and cimetidine. Pretreatment with cimetidine prior to intravenous fluorouracil increased the fluorouracil area under the concentration versus time curve (AUC) by 27%. The total body clearance was reduced by 28%. This may lead to increased plasma concentrations of fluorouracil.

Calcium folinate (leucovorin)

Leucovorin calcium enhances the binding of fluorouracil to thymidylate synthase, which may lead to increased antitumour efficacy and toxicity of fluorouracil.

Warfarin

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

Brivudine and sorivudine

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

Levamisole

Combination therapy with fluorouracil and levamisole has been associated with multifocal inflammatory leukoencephalopathy (MILE). Symptoms may include memory loss, confusion, paraesthesia, lethargy, muscle weakness, speech disturbances, coma and seizures.

The cerebrospinal fluid may show mild pleiocytosis, and computed tomography and magnetic resonance scans may show lesions in the white matter suggestive of demyelination. If this syndrome occurs, treatment should be discontinued immediately.

The condition is at least partially reversible if fluorouracil and levamisole are discontinued, and corticosteroids given. The use of levamisole and fluorouracil is no longer recommended by NH&MRC 'Clinical Practice guidelines: The prevention, early detection and

management of colorectal cancer'. This combination regimen has been superseded by fluorouracil and leucovorin.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil. Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of CYP2C9 isoenzyme system by capecitabine. Serum levels of phenytoin sustained above the optimal range may produce encephalopathy, or confusional states (delirium psychosis), or rarely irreversible cerebellar dysfunction. Therefore, patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

Laboratory values

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

4.6 Pregnancy, fertility and Lactation

Pregnancy

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

Fluorouracil is strictly contraindicated in pregnant and breastfeeding women.

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. 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.

Fertility

Men treated with Fluorouracil are advised not to father a child during and for up to 6 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.

Effects of fluorouracil on the gonads and reproduction capacity of humans are not fully known. However, drugs which inhibit DNA, RNA, and protein synthesis (such as fluorouracil), presumably interfere with gametogenesis.

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 events of the nervous system and visual changes which could interfere with driving or the usage of heavy machinery.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with Fluorouracil Injection with the following frequencies:

Very common (≥1/10),

Common (≥ 1/100 to < 1/10),

Uncommon (≥ 1/1,000 to < 1/100),

Rare (≥ 1/10,000 to < 1/1,000),

Very rare (< 1/10,000),

Frequency not known (cannot be estimated from the available data).

Infections and infestations:	
Very common	Infections
Blood and lymphatic system disorders:	
Very common	Myelosuppression (leucopenia, pancytopenia and thrombocytopenia); agranulocytosis, anaemia

Common	Febrile neutropenia
Immune system disorders:	
Very common	Bronchospasm, Immunosuppression with an increased risk of infection.
Rare	Hypersensitivity reactions, generalised anaphylactic and allergic reactions.
Psychiatric disorders:	
Uncommon	Euphoria
Rare	a reversible confusional state may occur
Very rare	Disorientation
Nervous system disorders	
Uncommon	Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, and somnolence
Very rare	Cases of leukoencephalopathy have also been reported. With symptoms including ataxia, acute cerebellar syndrome, dysarthria, myasthenia, aphasia, convulsion or coma in patients receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency, kidney failure
Frequency not known	Peripheral neuropathy may occur, Hyperammonaemic

	encephalopathy
Eye disorders:	
Uncommon	Incidences of excessive lacrimation, dacryostenosis, visual changes and photophobia.
Cardiac disorders	
Very common	ECG changes
Common	Angina pectoris-like chest pain

Uncommon	Arrhythmia, myocardial infarction, myocardial ishchaemia, dilative cardiomyopathy
Very rare	Cardiac arrest and sudden cardiac death
Frequency not known	Pericarditis, tachycardia, breathlessness
Special attention is therefore advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.	
Vascular disorders:	
Rare	Cerebral, intestinal and peripheral ischemia, Reynaud's syndrome, thromboembolism, thrombophlebitis
Uncommon	Hypotension
Gastrointestinal disorders:	
Very common	Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An antiemetic may be given for nausea and vomiting. Additionally, events of anorexia, stomatitis (symptoms include soreness, erythema or ulceration of the oral cavity or dysphagia); proctitis, oesophagitis
Uncommon	Gastrointestinal ulcerations and bleeding (may result in therapy being discontinued)
Skin and subcutaneous tissue disorders:	
Very common	Alopecia may be seen in a substantial number of cases particularly in females, but is reversible. Palmar-plantar erythrodysesthesia syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil. 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	Other side effects include dermatitis, pigmentation, changes in the nails (e.g. diffuse superficial blue pigmentation,

	hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia), dry skin, fissure erosion, erythema, pruritic maculopapular rash, exanthema, photosensitivity, hyperpigmentation of the skin, streaky hyperpigmentation or depigmentation near the veins.
General disorders and administration site conditions	
Very Common	Malaise, weakness
Frequency 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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

Patients in which an overdose of fluorouracil is detected should be closely monitored haematologically for at least 4 weeks.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; Antimetabolites;

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 can also be incorporated into RNA, resulting in formation of defective RNA.

5.2 Pharmacokinetic properties

Absorption and Distribution

After intravenous administration, Flourouracil 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 ready enters the C.S.F and brain tissue.

Biotransformation

5-fluorouracil is catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5fluoro-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 5fluorouracil.

Elimination

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

Special populations

In patients with hepatic or renal failure, biotransformation and/or elimination of fluorouracil is reduced, requiring a reduction in dose rate.

5.3 Preclinical safety data

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

6. Pharmaceutical Particulars

6.1 List of Excipients

Tris (Hydroxymethyl) Aminomethane

Sodium Hydroxide

Water for Injections

6.2 Incompatibilities

Admixtures with acidic drugs or drugs that are unstable in the presence of alkali should be avoided. Fluorouracil is reported to be incompatible with cytarabine, diazepam, methotrexate, platinum compounds, doxorubicin (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate (leucovorin).

6.3 Shelf-Life

02 Years

6.4 Special Precautions for storage

Do not store above 25° C. Do not refrigerate or freeze. Keep container in the outer carton

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

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

6.5 Nature and Content of container

Type 1 clear glass vial (CGV) with rubber closures

Type 1 clear Onco-Tain® with rubber closures

Type 1 glass, Onco• Vial® with rubber closures

CGV and Onco-Tain® :

250 mg/5 ml: Pack Size 5.

500 mg/10 ml: Pack Size 5.

1 g/20 ml: Pack Size 5

2.5 g/50 ml: Pack Size 10's

5 g/100 ml: Pack Size singles

Onco-Vial® :
500 mg/10 ml: Pack Size singles
1 g/20 ml: Pack Size singles
2.5 g/50 ml: Pack Size singles

6.6 Special precautions for disposal and other handling

Cytotoxic Handling Guidelines

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

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. A bland cream 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.

Please refer to company for COSHH hazard datasheets.

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 under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal

Syringes, Onco• Vials® and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700° C.

Diluents

Fluorouracil Injection may be diluted with Glucose 5% Injection or Sodium Chloride 0.9% Injection or Water for Injections immediately before parenteral use.

Directions for use of the Onco• Vial®

Onco• Vial® should be used with an appropriate Mayne administration device.

7. Marketing Authorization Holder
Beacon Pharmaceuticals Limited

8. Marketing Authorization Number
CTD 10517

9. Date of first authorization/renewal of the authorization
20/12/2023

10. Date of revision of the text
14/05/2025