NEW ZEALAND DATA SHEET
FLUOROURACIL ACCORD (FLUOROURACIL) INJECTION

1 PRODUCT NAME

Fluorouracil Accord 50 mg/mL injection solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluorouracil Accord injection solution contains fluorouracil as the active ingredient. Five strengths are available as follows: 250 mg/5 mL, 500 mg/10 mL, 1 g/20 mL, 2.5 g/50 mL and 5 g/100 mL. The 2.5 g/50 mL and 5 g/100 mL vials are Pharmacy Bulk Packs.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Fluorouracil Accord Solution for Injection is a clear, colourless to slightly pale yellow solution containing fluorouracil for use as an intravenous infusion or injection. The pH of the fluorouracil injection solution is approximately 8.9.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Alone or in combination, for the palliative treatment of malignant tumours, particularly of the breast, colon or rectum; and in the treatment of gastric, primary hepatic, pancreatic, uterine (cervical particularly), ovarian and bladder carcinomas.

Fluorouracil should only be used when other proven measures have failed or are considered impractical.

4.2 DOSE AND METHOD OF ADMINISTRATION

General directions

Fluorouracil Accord contains no antimicrobial agent. The product is for single use in one patient only. Discard any residue.

The use of the Pharmacy Bulk Pack should be restricted to suitably qualified pharmacists operating in suitably equipped hospital pharmacies or compounding centres. The Pharmacy Bulk Pack is intended for multiple dispensing but should be spiked only once.

To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours after preparation. Administration should be completed within 24 hours of preparation of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs (see **Handling Precautions** and **Spills and Disposal**).

Fluorouracil Injection may be administered by intravenous infusion or intravenous injection, the dosage being based on the patient's actual weight. Ideal weight is used only if the patient is obese or if there has been a spurious weight gain due to oedema, ascites or other forms of abnormal fluid retention. Prior to treatment, each patient is to be carefully evaluated in order to estimate the optimum initial dosage of fluorouracil.

The total daily dose of fluorouracil should not exceed 1 g. The initial recommended doses should be reduced by one-third to one-half if any of the following conditions are present: poor nutritional state; within 30 days after major surgery; inadequate bone marrow function (white blood cell count $< 5{,}000/mm^3$, platelet count $< 100{,}000/mm^3$); impaired hepatic and/or renal function.

The following regimens have been recommended for use of fluorouracil as a single agent in adults.

Intravenous Infusion

15 mg/kg bodyweight (to a maximum of 1 g) daily diluted in 300 to 500 mL of 5% glucose given over a period of four hours. Infusions may be continued daily until the first gastrointestinal side effects occur, i.e. stomatitis, diarrhoea, leucopenia, thrombocytopenia; treatment should then be discontinued. After the side effects have subsided and the WBC count has risen to 3,000 to 4,000/mm^3 or the platelet count to 80,000 to 100,000/mm^3 the patient may then be placed on a maintenance therapy program.

Intravenous Injection

12 mg/kg bodyweight daily for three consecutive days. If toxic effects do not appear, the patient may then be given 6 mg/kg intravenously on the 5th, 7th and 9th days. If there are still no signs of toxicity, the patients may be placed on maintenance therapy, otherwise regression of toxic side effects must be awaited before continuing therapy.

Maintenance Therapy

5 to 10 mg/kg bodyweight by intravenous injection once a week. Toxic effects seldom occur during maintenance therapy. If, however, they do appear, therapy must be discontinued until the symptoms regress, otherwise regression of toxic side effects must be awaited before continuing therapy.

Other Methods of Administration

Fluorouracil Accord may be used in combination with other cytostatic agents or with radiotherapy; in such cases, doses should be reduced accordingly. Administration of 5-7 mg/kg bodyweight daily may also be performed as a 24 hour intra-arterial continuous drip infusion.

Compatibilities

Fluorouracil Accord is compatible with the following infusion media: 0.9% sodium chloride, 5% glucose, 0.9% sodium chloride with 5% glucose.

Fluorouracil Accord can be used in combination with other antitumour agents, but it is not recommended that it be mixed with these drugs in the same container.

4.3 CONTRAINDICATIONS

Fluorouracil is contraindicated in patients:

- who have any known hypersensitivity to fluorouracil,
- who are debilitated,
- who are suffering a poor nutritional state,
- who are suffering from bone marrow depression following radiotherapy or therapy with other antineoplastic agents (leucocyte count less than 5,000/mm^3, platelet count less than 100,000/mm^3),
- who are suffering from a potentially serious infection,
- who are pregnant
- with known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see **Section 4.4 Special Warnings and Precautions for Use**).

Fluorouracil must not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues. Brivudine, sorivudine and their analogues are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD), which degrades fluorouracil (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interaction**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluorouracil should be administered only by or under strict supervision of a qualified physician experienced in therapy with potent metabolites and only when the potential benefits of fluorouracil outweigh the possible risks. Because of the possibility of severe toxic reactions, all patients should be hospitalised, at least during the initial course of therapy and appropriate facilities should be available for adequate management of complications should they arise.

Fluorouracil should not be re-administered after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death.

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

Toxicity

Fluorouracil has a narrow margin of safety and is a highly toxic drug. The most pronounced and dose-limiting toxic effects of fluorouracil are on the normal, rapidly proliferating tissues of the bone marrow and the lining of the gastrointestinal tract. Fluorouracil therapy should be discontinued promptly whenever one of the following signs of toxicity appears: leucopenia, thrombocytopenia, stomatitis, oesophagopharyngitis, intractable vomiting, diarrhoea, melaena, haemorrhage, oral ulceration, evidence of gastrointestinal ulceration or bleeding.

Rarely, severe and unexpected toxic reactions (including stomatitis, diarrhoea, neutropenia and neurotoxicity) have been reported in association with fluorouracil. These reactions have been attributed to deficiency of dipyrimidine dehydrogenase activity, which appears to cause prolonged clearance of fluorouracil.

Any form of therapy that adds to the stress of the patient, interferes with nutritional uptake or depresses bone marrow function will increase the toxicity of fluorouracil.

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.

Cardiotoxicity

Fluorouracil administration has been associated with myocardial ischaemia, cardiomyopathy and, very rarely, sudden death. Angina, tachycardia, breathlessness, arrhythmia, ECG abnormalities, myocardial infarction and stress cardiomyopathy (Takotsubo Syndrome) have been reported after administration of fluorouracil. Attention should therefore be paid to patients who experience chest pain during treatment, and patients with a history of heart disease. There is an increased risk of death associated with re-administration of fluorouracil in patients with a documented cardiovascular reaction to fluorouracil (see **Section 4.8 Undesirable Effects**).

Myelosuppression

Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to leucopenia, granulocytopenia, pancytopenia, and thrombocytopenia). Leucopenia and thrombocytopenia commonly follow treatment of fluorouracil.

The initial dose should be reduced, or treatment should not be started in the presence of diminished leucocytes and/or platelets (see **Sections 4.3 Contraindications and 4.2 Dose and Method of Administration**).

Leucopenia occurs after nearly every treatment period with an effective dose. The nadir for white blood cell count usually occurs from the 9th to the 14th day after initiation of therapy, but may occur as late as the 20th day. The count usually returns to normal by the 30th day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the 7th to the 17th day of therapy.

Daily monitoring of platelet and white blood cell counts is recommended. Treatment with fluorouracil should be discontinued if the leucocyte count falls rapidly or if it falls below 3,500/mm^3, or if there is a fall in the platelet count below 100,000/mm^3. If the leucocyte count falls below 2,000/mm^3, the patient should be placed in an isolation unit and given an appropriate preventative treatment for systemic infection.

Clinical consequences of severe myelosuppression include infections. Viral, bacterial, fungal and/or parasitic infections, either localized or systemic, may be associated with the use of fluorouracil alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal.

Gastrointestinal effects

Loss of appetite, nausea and vomiting are common adverse effects, which generally occur during the first week of therapy. These adverse effects may be treated symptomatically and can often be alleviated by antiemetics. Stomatitis is one of the most common and often the earliest sign of specific toxicity, appearing as early as the fourth day, but more commonly on the fifth to eighth day of therapy. Diarrhea is also a common adverse effect. It is usually mild and usually occurs later in treatment. Severe diarrhea may also be accompanied by dehydration and melena.

Combination chemotherapy/radiotherapy

May depress bone marrow function and increase the toxicity of fluorouracil. Extreme caution is necessary when administering fluorouracil to patients who have had high dose pelvic irradiation or have been previously treated with alkylating agents and in those who have a widespread involvement of bone marrow by metastatic tumours. Radiation therapy on the bone marrow, especially to the area of the chest and mediastinum, may potentiate the bone marrow effects of fluorouracil. Fluorouracil treatment may potentiate necrosis caused by radiation. Concomitant use of other chemotherapeutic agents may depress bone marrow function and increase the toxicity of fluorouracil.

Dihydropyrimidine dehydrogenase (DPD) deficiency

Rare cases of severe stomatitis, diarrhoea, neutropenia and neurotoxicity have been associated with fluorouracil exposure in patients with a deficiency in DPD activity.

Patients who have an absent or low activity of DPD (dihydropyrimidine dehydrogenase is an enzyme involved in the degradation of fluorouracil) are at an increased risk of life-threatening, fatal or severe adverse reaction. DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

It is recommended that DPD status of the patient is determined before therapy through laboratory testing for the detection of total or partial DPD-deficiency, where testing is available. It can also be useful when evaluating patients experiencing fluorouracil-related toxicities.

It has been established that patients with specific homozygous or compound heterozygous mutations in the gene locus for DPYD (i.e. c.1236G>A/HapB3, DPYD*2A, c.2846A>T, and c.1679T>G variants) can result in near complete absence or total absence of DPD enzymatic activity (as per laboratory assays) These patients have the highest risk of fatal toxicity or life threatening toxicity – and should NOT be administered fluorouracil (see **Sections 4.3 Contraindications**).

For those patients with a complete absence of DPD (dihydropyrimidine dehydrogenase) activity, no dose has been proven safe.

Patients with specific heterozygous DPYD variants (i.e. c.1236G>A/HapB3, DPYD*2A, c.2846A>T, and c.1679T>G variants) when treated with fluorouracil, have an increased risk of severe toxicity.

There is around 1% frequency in Caucasian patients of the heterozygous DPYD*2A genotype in the DPYD gene, 0.07 to 0.1% for c.1679T>G1, 2.6 to 6.3% for c.1236G>A/HapB3 and 1.1% for c.2846A>T variants. Data in populations other than Caucasian, on the frequency of these DPYD variants is limited. Other rare variants cannot be excluded that also may be associated with an increased risk of severe toxicity.

For patients with partial DPD (dihydropyrimidine dehydrogenase) deficiency (with heterozygous DPYD gene mutations) where the benefits of fluorouracil are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity. To avoid serious toxicity, a reduction of the starting dose should be considered in these patients. In patients with partial DPD activity (as measured by specific test), there is not sufficient data for a specific dose to be recommended.

It has been reported that there has been a greater risk of side effects reported with c.1679T>G and DPYD*2A, gene variants due to a greater reduction in enzymatic activity than the other variants. With reduced doses the effects on clinical efficacy are uncertain at this time. Therefore, in the absence of serious toxicity the dose could be increased, while carefully monitoring the patient.

For patients who have had a negative test for the above-mentioned alleles, there is still a risk of adverse events that are severe.

In patients with unrecognised DPD deficiency treated with fluorouracil as well as in those patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of 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.

Immunosuppressant effects/ increased susceptibility to infections

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents including fluorouracil, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving fluorouracil. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Compatibilities

See **Section 4.2 Dose and Method of Administration, Compatibilities**.

Photosensitivity reactions

Some patients may experience photosensitivity reactions following administration of fluorouracil, it is recommended that patients are warned to avoid prolonged exposure to sunlight (see **Section 4.8 Undesirable Effects).**

Monitoring phenytoin levels

Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

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 characterised 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.

Multifocal inflammatory leucoencephalopathy (MILE)

Combination therapy with fluorouracil and levamisole has been associated with multifocal inflammatory leucoencephalopathy (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.

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.

Use in hepatic impairment

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

Use in renal impairment

Fluorouracil should be used with caution in patients with reduced renal function or heart disease.

Use in the elderly

Fluorouracil should be used with caution in elderly patients. An age of 70 years or older and the female gender are statistically significant risk factors for severe toxicity from fluorouracil based chemotherapy. These effects may be additive in older women. While advanced age does not contraindicate the use of this type of chemotherapy, close monitoring for multiple organ toxicities and vigorous supportive care of those with toxicity are required.

Paediatric use

No data available.

Effects on laboratory tests

Fluorouracil could interfere with diagnostic tests of thyroid function by causing rises in total thyroxine and liothyronine due to increased globulin binding. Plasma albumin may be decreased because of drug-induced protein malabsorption.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Cytotoxic agents: All myelosuppressive drugs (e.g. cytotoxic agents used in combination chemotherapy) can increase haematotoxicity of fluorouracil.

Folinic acid (leucovorin) enhances the DNA-directed toxicity of fluorouracil. This combination should be used with caution as the toxicity of fluorouracil, especially GI and haematologic, may be increased. Careful monitoring should be observed and the dose of fluorouracil may be decreased based on current guidelines.

Allopurinol may decrease the degree of bone marrow depression produced by fluorouracil. Studies of this possibility have reported conflicting results.

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil. Common medicines include methotrexate, metronidazole and folinic acid (leucovorin).

Metronidazole: Metronidazole may enhance the toxicity of fluorouracil. The mechanism of interaction is presumed to be reduced clearance of fluorouracil by metronidazole. Concurrent administration should be avoided.

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 superceded by fluorouracil and folinic acid.

Pre-treatment with cimetidine prior to intravenous fluorouracil increased the area under the concentration time curve (AUC) by 27%. The total body clearance was reduced by 28%. This may lead to increased plasma concentrations of fluorouracil. This effect is probably due to both inhibition of

hepatic enzymes and reduction of hepatic blood flow. Caution should be taken if the patient receives fluorouracil and cimetidine concurrently.

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 and the phenytoin dosage may need to be reduced.

Brivudine and sorivudine: Brivudine, sorivudine or their chemically related analogues irreversibly inhibit DPD, resulting in a significant increase in fluorouracil exposure. This may lead to increased fluoropyrimidine-related toxicities with potentially fatal outcome. Therefore, either a different antiviral therapy may be used or there should be an interval of at least 4 weeks between the administration of brivudine, sorivudine, or the analogues and the start of fluorouracil treatment (see **Section 4.3 Contraindications**). 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 hospitalisation is recommended.

Radiation therapy: Radiation therapy on the bone marrow, especially to the area of the chest and mediastinum, may potentiate the bone marrow effects of fluorouracil.

Warfarin: Elevated INR levels and occasional episodes of bleeding have been reported during concomitant use of warfarin and fluorouracil or its analogues. In these cases, fluorouracil has usually been administered as one component of an antineoplastic combination regimen. Adequate anticoagulant response to warfarin and other coumarin-derivative therapy should be monitored regularly in patients taking fluorouracil. 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.

Live or live-attenuated vaccines: Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents including fluorouracil, may result in serious or fatal infections. (see **Section 4.4 Special Warnings and Precautions of Use**).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fluorouracil has not been adequately studied in animals to permit an evaluation of its effects on fertility and general reproductive performance. However, doses of 125 or 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organisation of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil did not produce any abnormalities at oral doses of up to 80 mg/kg/day. In female rats, fluorouracil, administered intraperitoneally at weekly doses of 25 or 50 mg/kg for three weeks during the pre-ovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of pre-implantation lethality and induced chromosomal anomalies in these embryos. In a limited study in rabbits, a single 25 mg/kg dose of fluorouracil or 5 daily doses of 5 mg/kg had no effect on ovulation, appeared not to affect implantation and had only limited effect in producing zygote destruction. Compounds such as fluorouracil which interfere with DNA, RNA and protein synthesis might be expected to have adverse effects on gametogenesis. In general, use of a contraceptive is recommended during cytotoxic therapy.

Use in pregnancy (Category D)

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Fluorouracil may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats and hamsters, and embryolethal in monkeys. Fluorouracil is strictly contraindicated in pregnancy. Safety for use in pregnancy has not been established. Women of childbearing age should be advised to avoid pregnancy during fluorouracil therapy. Fluorouracil should only be used in women of child bearing potential if the expected benefits outweigh the risks of therapy, and adequate contraception is used. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazards to the foetus.

Men undergoing fluorouracil treatment should also ensure they use effective contraception measures.

Use in lactation

It is not known whether fluorouracil is excreted in breast milk. To avoid possible harmful effects in the infant, breastfeeding is not advised during fluorouracil therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 UNDESIRABLE EFFECTS

The ratio between effective and toxic dose is small and therapy with fluorouracil is usually accompanied by some degree of adverse effects. Patients should be very carefully observed and dosage adjustment may have to be made. Deaths have been reported.

Gastrointestinal

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.

Nausea and vomiting occur and may be treated symptomatically.

Stomatitis is usually an early sign of impending severe toxicity which may be evident after five to eight days of therapy. Symptoms include soreness, erythema or ulceration of the oral cavity or dysphagia. Other reported gastrointestinal symptoms are diarrhoea, proctitis, melaena, gastrointestinal haemorrhage, gastrointestinal ulcer and oesophagitis, therefore, the dose may require adjustment or therapy may need to be discontinued. Gastrointestinal side effects may be exacerbated if fluorouracil is given with folinic acid (leucovorin).

Dermatological

Alopecia[a] may be seen in a substantial number of cases, but it is reversible. Nail disorders[b], dermatitis[c], cutaneous lupus erythematosus and hyperpigmentation of the nail beds and other body areas[d] have been reported. Skin rashes and fissures have been associated with fluorouracil therapy. Palmar-plantar erythrodysaesthesia syndrome[e], thrombophlebitis and asymptomatic hyperpigmentation over vascular channels have also been reported. Continuous-infusion fluorouracil may increase incidence and severity of palmar-plantar erythrodysaesthesia, photosensitivity reactions.

Haematological

Leucopenia, primarily granulocytopenia, commonly occurs. The nadir for white blood cell count usually occurs from the ninth to the fourteenth day after initiation of therapy, but may occur as late as the twenty-fifth day. The count usually returns to normal by the thirtieth day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the seventh to the seventeenth day of therapy. Bone marrow failure and pancytopenia may also occur.

Cardiovascular

Fluorouracil administration has been associated with cardiac shock[f], cardiac failure[f], myocarditis[f], angina pectoris[f,g], myocardial ischaemia[f], myocardial infarction[f], cardiomyopathy[f], pericarditis[f], thrombophlebitis and haemorrhage. There have been reports of chest pain, tachycardia[f], breathlessness, arrhythmia[f], and ECG changes (ST segment changes) after administration of fluorouracil. There have been reports of sudden death in patients readministered fluorouracil after a documented cardiovascular reaction.

Ophthalmic

Systemic fluorouracil treatment has been associated with various types of ocular toxicity. Additionally, several other reports have been noted including excessive lacrimation, dacryostenosis, visual changes and photophobia.

Neurological

Combination therapy with fluorouracil and levamisole has been associated with Leukoencephalopathy[h] and multifocal inflammatory leucoencephalopathy (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.

Neurotoxicity[h]: Disorientation, confusion, euphoria, ataxia, nystagmus, headache, slurred speech, dizziness, unsteadiness, muscular weakness, acute cerebellar syndrome and occasionally oculomotor disturbances have occurred in patients receiving fluorouracil. These symptoms may persist after therapy is discontinued.

Infections and infestations

Septic shock, sepsis, neutropenic sepsis, progressive multifocal leukoencephalopathy, pneumonia, superinfection, urinary tract infection, catheter related infection, cellulitis, pharyngitis, and other infections.

Metabolism and nutrition disorders

Dehydration, decreased appetite, tumour lysis syndrome.

Immune system disorders

Anaphylactic reaction, hypersensitivity.

Other

Local injection site reaction. Fever has also been reported. Rarely, anaphylaxis or generalised allergic reactions have occurred in patients receiving fluorouracil. Pyrexia and chest pain. Haemorrhage and thromobophlebitis have occurred.

a Reversible
b Such as partial or complete detachment of nails
c Manifests often as itchy maculopapular rash on the extremities
d Skin hyperpigmentation also refers to asymptomatic hyperpigmentation over vascular channels
e Observed in patients who received fluorouracil and leucovorin bolus administration
f Listed cardiac disorders associated with fluorouracil may lead to cardiac arrest
g Observed in patients receiving high dose leucovorin and fluorouracil bolus and continuous infusion
h Symptoms may persist after therapy is discontinued

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. In New Zealand, healthcare

professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Signs and Symptoms

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; the anticipated manifestations include nausea, vomiting, diarrhoea, gastrointestinal ulceration, haemorrhage and bleeding, and bone marrow depression (including thrombocytopenia, leucopenia, granulocytopenia and agranulocytosis).

Treatment

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

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. Fluorouracil itself is inactive and is converted intracellularly to active metabolites. After 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

After intravenous administration, fluorouracil is distributed throughout body tissues and fluids. The plasma half-life is 8 to 22 minutes and is dose dependent. Fluorouracil disappears from the blood within four hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil readily enters the cerebrospinal fluid (CSF).

Metabolism and Excretion

About 20% is excreted unchanged in the urine and the remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fluorouracil has been shown to be mutagenic and clastogenic in a number of studies. Oncogenic transformation of fibroblasts from mouse embryo has been induced *in vitro* by fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. A positive effect was observed in the micronucleus test on bone marrow cells of the mouse, and fluorouracil at very high concentrations produced chromosomal breaks in hamster fibroblasts *in vitro.*

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of fluorouracil have not been performed. However, there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses 0.01, 0.3, 1 or 3 mg per rat 5 days per week for 52 weeks, followed by a 6 month observation period. On the basis of the available data, no evaluation can be made of the carcinogenic risk of fluorouracil to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Fluorouracil Accord injection solution contains water for injection. Hydrochloric acid and sodium hydroxide are used to adjust pH.

6.2 INCOMPATIBILITIES

Admixtures with acidic medicines or medicines that decompose in an alkaline environment 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) or levoleucovorin calcium.

6.3 SHELF LIFE

24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate. Do not freeze. Protect from light.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Five strengths are available as follows: 250 mg/5 mL, 500 mg/10 mL, 1 g/20 mL, 2.5 g/50 mL and 5 g/100 mL in glass vials in packs of 1.

The 2.5 g/50 mL and 5 g/100 mL vials are Pharmacy Bulk Packs.

Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Handling Precautions

As with all antineoplastic agents, trained personnel should prepare Fluorouracil Accord. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling fluorouracil. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed, thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as fluorouracil.

Luer-Lok fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare Fluorouracil Accord, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerated at 1,100°C.

Spills and disposal

If spill occurs, restrict access to the affected area. Wear two pairs of latex rubber gloves, a suitable mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towels or adsorbent granules. Spills may also be treated with sodium hypochlorite

5%. Collect the absorbent/adsorbent and other debris from the spill and place in a leakproof plastic container and label accordingly. Cytotoxic waste should be regarded as toxic and hazardous and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1,100°C'. Waste material should be incinerated at 1,100°C for at least one second. Clean the remaining spill area with copious amounts of water.

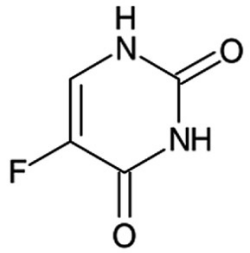
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: 5-fluoro-1H, 3H-pyrimidine-2, 4-dione.

Molecular formula: $C_4H_3FN_2O_2$.

Molecular weight: 130.1.

Chemical structure



CAS number

51-21-8

7 MEDICINE SCHEDULE

S4 - Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

09 July 2020

10 DATE OF REVISION OF THE TEXT

11 January 2023

Version 5.0

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of stress cardiomyopathy (Takotsubo syndrome) and tumour lysis syndrome
4.8	Addition of tumour lysis syndrome, cutaneous lupus erythematosus and stress cardiomyopathy. Minor editorial changes.