Teva Pharmaceuticals (Pty) Ltd	**Product: FLURACEDYL 250/500/5000/1000/500 mg** **Strength:** Each ml contains 50 mg of 5-fluorouracil as the sodium salt. **Dosage Form:** solution for injection

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

FLURACEDYL 250 mg

FLURACEDYL 500 mg

FLURACEDYL 1000 mg

FLURACEDYL 5000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each ml contains 50 mg of 5-fluorouracil as the sodium salt.

Excipients with known effect:

FLURACEDYL contains sodium. This should be taken into consideration by patients on a sodium controlled diet.

3. PHARMACEUTICAL FORM:

Solution for injection.

Clear, colourless to almost colourless solution, free from particles.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Palliative management of cancer of the breast and gastrointestinal tract.

4.2 Posology and method of administration:

FLURACEDYL can be given as an IV infusion or as an IV injection. Precipitation in solution can be dissolved by heating to 35 ºC.

The recommended dose for average risk patients in good nutritional status with adequate haematopoietic, renal and hepatic function is 12 mg/kg daily for 4 days, by rapid injection, followed by 6 mg/kg on alternate succeeding days for two to four doses, if no toxicity is observed.

The maximal daily dose has been established at about 800 mg.

Treatment should be discontinued at the earliest manifestation of toxicity (usually stomatitis or diarrhoea), because the maximal effects of bone marrow suppression will not be evident until the ninth to fourteenth day.

The first course of therapy should be administered either in the hospital or under extremely close supervision in order to establish the tolerance of the individual patient.

After a period of four weeks from the first injection of the preceding course, a new course of therapy is initiated; the dosage is adjusted on the basis of the previous response and is repeated at monthly intervals.

Another type of maintenance schedule is 10 to 15 mg/kg or 500 to 600 mg/m^2, administered weekly as a single rapid injection.

It is usually necessary to produce mild to moderate toxicity in order to achieve significant antineoplastic effects.

FLURACEDYL may also be given by intravenous infusion, usual doses of 15 mg/kg daily being infused in 500 ml of 0,9 % sodium chloride or 5 % glucose injection over 4 hours and repeated on successive days until toxicity occurs or a total of 12 to 15 g has been given. Continuous infusion may also be used. The course may be repeated after 4 to 6 weeks.

The white cell count should be determined frequently during treatment with FLURACEDYL and therapy stopped immediately if the count falls rapidly or falls below 3500/mm^3, if the platelet count falls below 100 000/mm^3, or if severe adverse events occur. Doses should be halved in patients with poor nutritional status, impaired bone marrow, hepatic, or renal function and after major surgery.

FLURACEDYL vials are for single dose use only and any unused portion of the solution must be discarded. The only exception is the 100 ml multidose vial, which may be kept for 8 hours after opening (see **section 6.4)**.

4.3 Contraindications:

- Hypersensitivity to 5–Fluorouracil or to any of the other ingredients of FLURACEDYL (see **section 2**).
- Bone marrow depression after radiotherapy or treatment with other antineoplastic medicines.
- Serious liver impairment.
- Serious infections (e.g. Herpes zoster, chickenpox).
- Recent or concomitant treatment with brivudine (see **section 4.4** and **section 4.5**)
- In patients with known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see **section 4.4**).
- Pregnancy and breastfeeding (see **section 4.6**).
- The use of live vaccines is contraindicated in patients receiving FLURACEDYL therapy.

4.4 Special warnings and precautions for use:

FLURACEDYL should be used with extreme caution in poor risk patients with a history of high dose pelvic irradiation or previous use of alkylating medicines, and those who have a wide-spread involvement of bone marrow by metastatic tumours.

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.

***Bone marrow failure*:**

Adequate treatment with FLURACEDYL is usually followed by leukopenia, the lowest white blood cell (WBC) count commonly being observed between the 7th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anaemia may also occur. Daily monitoring of platelet and WBC count is recommended and FLURACEDYL treatment should be stopped if platelets fall below 100 000 per mm^3 or the WBC count falls below 3 500 per mm^3. If the total count is less than 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.

The main adverse events are on the bone marrow and gastrointestinal tract. Reducing the rate of injection to a slow infusion can decrease haematological but not gastrointestinal toxicity. Leukopenia and thrombocytopenia are signs that FLURACEDYL treatment should be stopped.

***Gastrointestinal toxicity*:**

FLURACEDYL should be discontinued at the first sign of oral ulceration or if there is evidence of gastrointestinal (GI) side effects such as stomatitis, diarrhoea, bleeding from the GI tract or haemorrhage at any site.

Gastrointestinal toxicity may be exacerbated if FLURACEDYL is given with folinic acid (see **section 4.5**).

Gastrointestinal adverse events are frequent and may be life-threatening.

Also, FLURACEDYL is not intended to be used as an adjuvant to surgery.

FLURACEDYL should be given with care to those patients with a history of heart disease, or those with hepatic or renal insufficiency or jaundice.

***Cardiotoxicity*:**

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, myocarditis, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse events are frequent in patients receiving a continuous infusion of FLURACEDYL 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 FLURACEDYL treatment, or patients with a history of heart disease. Cardiac function should be regularly monitored during treatment with FLURACEDYL. In case of severe cardiotoxicity FLURACEDYL should be discontinued.

***Encephalopathy*:**

There has been post-marketing reports of encephalopathies (including hyperammonaemic encephalopathy, leukoencephalopathy) associated with 5-fluorouracil treatment. Signs or symptoms of encephalopathy are altered mental status, confusion, disorientation, coma or ataxia. If a patient develops any of these symptoms withhold FLURACEDYL treatment and test serum ammonia levels immediately. In case of elevated serum ammonia levels initiate ammonia-lowering therapy.

Caution is necessary when administering FLURACEDYL 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*:**

Testing for DPD deficiency:

Patients receiving FLURACEDYL must be tested for DPD deficiency before starting treatment.

Phenotype and/or genotype testing is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

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, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.

DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

A reduction of the starting dose in these patients to be considered to limit the risk of severe toxicity for patients with partial DPD deficiency (as they are at an increased risk of severe and potentially life-threatening toxicity). Subsequent doses may be increased in the absence of serious toxicity as the efficacy of a reduced dose has not been established.

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 this medicinal product (see **section 4.3**).

Partial DPD deficiency :

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

Genotypic characterisation of DPD deficiency:

Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency.

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

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

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

The frequency of the heterozygous c.1905+1G>A genotype in the DPYD gene in Caucasian patients is around 1 %; 1,1 % for c.2846A>T; 2,6-6,3 % for c.1236G>A/HapB3 variants and 0,07 to 0,1 % for c.1679T>G.

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

Phenotypic characterisation of DPD deficiency:

For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma is recommended.

Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level ≥ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.

5-Fluorouracil Therapeutic drug monitoring (TDM):

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

Brivudine must not be administered concomitantly with FLURACEDYL. Fatal cases have been reported following this medicine interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of FLURACEDYL therapy. Treatment with brivudine can be started 24 hours after the last dose of FLURACEDYL (see **section 4.3** and **section 4.5**)

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

***Photosensitivity*:**

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

***Contraception*:**

Women of childbearing potential and men have to use effective contraception during and up to at least 3 months after FLURACEDYL treatment (see **section 4.6**).

***Phenytoin*:**

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

***Palmar-plantar erythrodysaesthesia syndrome*:**

Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome, HFS) 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.

***Paediatric population*:**

The safety and effectiveness of FLURACEDYL in paediatric patients have not been established, therefore, its use is not recommended.

***Toxicity*:**

Since FLURACEDYL is a highly toxic medicine, it is recommended that both its administration and the treatment of any toxic effects be under the supervision of a registered medical practitioner who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. FLURACEDYL treatment should be stopped in case of severe toxicity.

4.5 Interaction with other medicines and other forms of interaction:

Various medicines have been reported to biochemically modulate the anti-tumour efficacy or toxicity of FLURACEDYL (e.g. metronidazole).

Metronidazole may increase the plasma level of 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil.

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

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

The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil. Nucleoside analogues, e.g. sorivudin, may induce an increase in plasma concentrations of 5-fluorouracil or other fluoropyrimidines accompanied by toxicological reactions. Therefore, a minimum time interval of 4 weeks between administration of FLURACEDYL and sorivudin should be kept. If applicable, determination of DPD enzyme activity is indicated prior to treatment with FLURACEDYL.

Brivudine: A clinically significant interaction between brivudine and FLURACEDYL, resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be administered concomitantly with FLURACEDYL (see **section 4.3** and **section 4.5**). There must be at least a 4-week waiting period between end of treatment with brivudine and start of FLURACEDYL therapy. Treatment with brivudine can be started 24-hours after the last dose of FLURACEDYL.

In combination with other myelosuppressive medicines, FLURACEDYL dosage adjustment is necessary. Concomitant or previous radiation therapy may require dosage reduction.

Both the efficacy and toxicity of 5-fluorouracil may be increased when 5-fluorouracil is used in combination with folinic acid. Special care should be exercised when FLURACEDYL is given with folinic acid (see **section 4.4**).

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

4.6 Fertility, pregnancy and lactation:

FLURACEDYL is contraindicated during pregnancy and lactation.

Women of childbearing potential should be advised not to become pregnant while on treatment with FLURACEDYL.

***Contraception in males and females*:**

Women of childbearing potential should be advised to avoid becoming pregnant and use an effective method of contraception during treatment with FLURACEDYL and at least 3 months afterwards (see **section 4.4**).

***Fertility*:**

Men treated with FLURACEDYL are advised not to father a child during and for at least 3 months following cessation of FLURACEDYL treatment (see **section 4.4**). Advice on conservation of sperm should be sought prior to FLURACEDYL treatment because of the possibility of irreversible infertility due to therapy with FLURACEDYL.

4.7 Effects on ability to drive and use machines:

FLURACEDYL may cause nausea and vomiting. Therefore patients should be advised to refrain from driving or using machines until the effects of FLURACEDYL are known. The ocular irritation caused by FLURACEDYL may also influence the ability to drive and use machines.

4.8 Undesirable effects:

***Infections and infestations*:**

Frequent: Infections, sepsis

***Blood and lymphatic system disorders*:**

Frequent: Febrile neutropenia

Frequency unknown: Bone marrow failure, neutropenia, thrombocytopenia, leukopenia, agranulocytosis, pancytopenia, anaemia

***Immune system disorders*:**

Frequency unknown: Generalised allergic reactions, anaphylactic reaction, anaphylactic shock

***Psychiatric disorders*:**

Frequency unknown: Confusional state, euphoric mood, disorientation

***Nervous system disorders*:**

Less frequent: Central neurotoxicity (notably cerebellar ataxia)

Frequency unknown: Nystagmus, headache, dizziness, extrapyramidal disorder, leukoencephalopathy (including ataxia, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma), peripheral neuropathy, hyperammonaemic encephalopathy

***Eye disorders*:**

Less frequent: Ocular irritation

Frequency unknown: Lacrimation increased, visual changes (including blurred vision and diplopia), photophobia

***Cardiac disorders*:**

Less frequent: Myocardial ischaemia, cardiac arrest

Frequency unknown: Angina pectoris, dysrhythmia, myocardial infarction, myocarditis, heart insufficiency, dilative cardiomyopathy, cardiac shock, sudden cardiac death, pericarditis

***Vascular disorders*:**

Frequency unknown: Thrombophlebitis, thromboembolism, hypotension

***Respiratory, thoracic and mediastinal disorders*:**

Frequency unknown: Epistaxis, dyspnoea, bronchospasm

***Gastrointestinal disorders*:**

Less frequent: Nausea and vomiting

Frequency unknown: Mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), diarrhoea, gastrointestinal ulceration, gastrointestinal mucosal exfoliation, gastrointestinal haemorrhage

***Skin and subcutaneous tissue disorders*:**

Less frequent: Effects on the skin including rashes, hyperpigmentation, alopecia

Frequency unknown: Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome), dry skin, skin fissures, erythema, photosensitivity reaction, vein pigmentation, nail disorder including loss of nails

***Reproductive system and breast disorders*:**

Frequency unknown: Spermatogenesis disorder, ovulation disorder

***General disorders and administration site conditions*:**

Frequency unknown: Mucosal inflammation, dehydration, injection site extravasation

***Investigations*:**

Frequency unknown: Thyroxine increased, tri-iodothyronine increased, ECG signs of myocardial ischaemia

4.9 Overdose:

Therapy must be discontinued promptly and supportive measures initiated whenever one of the following signs of toxicity appears:

Leukopenia (white blood cells under 3500/mm^3); thrombocytopenia (platelets under 100 000/mm^3); stomatitis; the first small ulceration of the inner margin of the lips is a signal for cessation of therapy; diarrhoea; frequent bowel movement of watery stools; gastrointestinal ulceration and bleeding; haemorrhage from any site, nausea and vomiting.

Therapeutic response to FLURACEDYL is unlikely without some evidence of toxicity; hence the limits of toxic effects must be closely supervised and therapy stopped promptly when the signs and symptoms of overdosage become evident.

Patients who have been exposed to an overdose of FLURACEDYL should be monitored haematologically for at least four weeks. Should abnormalities appear appropriate therapy should be utilised.

5. PHARMACOLOGICAL PROPERTIES:

A 26 Cytostatics

5.1 Pharmacodynamic properties:

5–Fluorouracil is a pyrimidine analogue, antineoplastic medicine which acts as an antimetabolite to uracil. 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. It can also interfere with RNA synthesis.

5.2 Pharmacokinetic properties:

5-Fluorouracil is usually administered parenterally since absorption after oral ingestion is unpredictable and incomplete.

Metabolic degradation occurs, particularly in the liver. Rapid intravenous administration of 5-fluorouracil produces plasma concentrations of 0,1 to 1,0 millimol/litre; plasma clearance is rapid ($t_{½}$ is between 10 to 20 minutes).

5-Fluorouracil readily enters the CSF, and concentrations of approximately 7 micromol/litre are reached within 30 minutes after intravenous administration. Values are sustained for approximately 3 hours and subside slowly during a period of 9 hours.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Water for injection.

6.2 Incompatibilities:

None

6.3 Shelf life:

Before opening: 24 months

Reconstituted product: 48 hours when reconstituted with 5 % glucose or saline solution.

The multidose 100 ml vial/infusion bottle may be kept for 8 hours after opening when stored at or below 25 °C.

6.4 Special precautions for storage:

Store at or below 25 °C and protect from light. Do not refrigerate or freeze.

Store in the original package.

The 5 ml, 10 ml and 20 ml vials are single dose containers and any unused portion should be discarded.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of the container:

FLURACEDYL 250 mg: 5 ml clear, colourless glass vials for single use.

FLURACEDYL 500 mg: 10 ml clear, colourless glass vials for single use.

FLURACEDYL 1000 mg: 20 ml clear, colourless glass vials for single use.

FLURACEDYL 5000 mg: 100 ml clear, colourless glass multidose vials or infusion bottles.

Each vial is packed in a clear PVC sleeve and packed into an outer cardboard carton.

6.6 Special precautions for disposal:

None.

7. THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City,

Midrand,

2090

8. REGISTRATION NUMBERS:

FLURACEDYL 250 mg: 35/26/0144

FLURACEDYL 500 mg: 35/26/0349

FLURACEDYL 1000 mg: 35/26/0350

FLURACEDYL 5000 mg: 35/26/0351

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of registration:

FLURACEDYL 1 000 mg and 5 000 mg: 05 September 2003

FLURACEDYL 250 mg and 500 mg: 25 July 2003.

10. DATE OF REVISION OF THE TEXT:

28 November 2020