SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

5-Fluorouracil 500 mg per 10 mL concentrate solution for injection
5-Flurouracil Sandoz 500 mg/10 mL

5-Fluorouracil 500 mg per 10 mL concentrate solution for injection
5-Flurouracil Sandoz 1 g/20 mL

2. Qualitative and quantitative composition

Each mL of solution contains 50 mg of 5-fluorouracil.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Concentrate solution for infusion.

A clear and colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

5-Fluorouracil is indicated as an adjuvant or palliative treatment of
- advanced colorectal cancer
- advanced stomach cancer
- advanced pancreatic cancer
- advanced and/or metastatic breast cancer
- advanced tumours in the head and neck area
- advanced cervical cancer

is used in adults.

4.2 Posology and method of administration

Treatment with 5-fluorouracil must only be implemented by physicians who are experienced in tumour therapy. During the initial phase, hospitalisation of the patient must be considered.
5-Fluorouracil is used in monochemotherapy and as a part of polychemotherapy. Since the method of administration and dosage recommendations for 5-fluorouracil vary widely, only the common reference values can be stated.

The exact dosage should be taken from treatment protocols which have proven effective in the treatment of the respective disease.

Dosage

Initial therapy for daily use:
- as an i.v. infusion
  15 mg/kg or 600 mg/m² for 4 hours daily - until the occurrence of adverse reactions.
- as an i.v. injection
  12 mg/kg or 480 mg/m² slowly i.v. (2 to 3 min.) on the 1st, 2nd and 3rd day; if no signs of toxicity are detectable - administration of 6 mg/kg or 240 mg/m² on the 5th, 7th and 9th day.

Initial therapy for weekly use:
15 mg/kg or 600 mg/m² once weekly, slowly, i.v.

Maintenance therapy:
As soon as remission has been achieved and after abatement of the adverse reactions and renewed increases in leukocytes to 3,000–4,000/µl, platelets to 80,000–100,000/µl: 5-10 mg/kg or 200-400 mg/m² i.v. once weekly.

The maximum daily dosage of 1 g must not be exceeded.

All dosage information refers to the normal weight, meaning that in case of obesity, ascites or oedema, appropriate standardisation must be carried out.

The treatment duration is determined by the experienced specialist or as per the treatment protocol in accordance with the type and course of the disease.

If 5-fluorouracil is combined with other cytostatics which have a similar adverse reaction profile, or with radiotherapy, the dose must be reduced accordingly. Administration can take place in the form of a 24-hour continuous drip infusion.

Method of administration
For intravenous use.

5-fluorouracil must only be applied intravenously. It can be injected or infused after being diluted with a NaCl 0.9% solution or 5% glucose. Extravasal administration must be avoided.

Special dosage recommendations
The recommended doses are reduced by one-third to half in case of poor nutritional condition of the patient, after major surgery, in the case of myelosuppression (leukocytes < 4,000/µl, platelets < 100,000/µl) and severely impaired liver and kidney function.

Renal or hepatic impairment
Caution is advised and, if necessary, the dose must be reduced in patients with renal or hepatic impairment.

Elderly persons (aged 65 years and older)
It is not necessary to adjust the initial dosage. However, close monitoring of elderly patients is recommended.

4.3 Contraindications
5-fluorouracil must not be given in the event of:
- hypersensitivity to the active substance or any of the excipients listed in Section 6.1
- severe blood count changes
- bone marrow suppression
- haemorrhage
- severe renal and/or hepatic impairment
- acute, severe infections (e.g., herpes zoster, varicella)
- stomatitis

- ulcers of the oral cavity and gastrointestinal tract
- pseudomembranous enteritis
- patient in a poor general state of health
- during pregnancy and breast-feeding (see section 4.6)
- in patients with known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4)
- recent, concurrent, or planned (within four weeks) treatment with brivudine. The interaction between brivudine and fluoropyrimidines (e.g., capecitabine, 5-fluorouracil [5-FU], etc.) is potentially fatal (see also sections 4.4, 4.5 and 4.8).

Brivudine is a potent inhibitor of the 5-fluorouracil-degrading enzyme dihydropyrimidine dehydrogenase (DPD).

In patients with dihydropyrimidine dehydrogenase deficiency, normal 5-fluorouracil doses trigger increased adverse reactions. If serious adverse reactions occur, monitoring of the DPD activity can be appropriate. Patients with dihydropyrimidine dehydrogenase deficiency must not be treated with 5-fluorouracil.

Vaccinations with live vaccines must not be implemented in a temporal connection with 5-fluorouracil treatment. Any contact with poliomyelitis vaccines should be avoided.

4.4 Special warnings and precautions for use

Precautions for handling and using 5-fluorouracil
Due to possible mutagenic and carcinogenic effects, increased safety measures apply to hospital staff and physicians. During the handling of 5-fluorouracil, any contact with the skin and mucous membranes must be avoided, otherwise, immediate cleaning with water and soap is necessary. If the eyes are contaminated, they must be immediately rinsed with water and medical attention must be sought. All precautions must be taken to enable absolutely aseptic work. The use of a working area with laminar flow is recommended. Protective clothing must be worn while handling 5-fluorouracil.

Pregnant personnel must not work with 5-fluorouracil.

Therapeutic drug monitoring (therapeutic drug monitoring, TDM)
5-Fluorouracil TDM may improve clinical outcomes in patients receiving continuous infusions of 5-fluorouracil by reducing toxicity and increasing efficacy. The AUC should be between 20 and 30 mg x h/l.

Cardiotoxicity
Treatment with fluoropyrimidines was associated with cardiotoxicity, including myocardial infarction, angina pectoris, arrhythmia, myocarditis, cardiogenic shock, sudden death and changes in the ECG (including very rare cases of prolongation of the QT interval). These adverse reactions occur more frequently in patients who receive a continuous infusion with 5-fluorouracil than those receiving bolus injections. A known history of coronary heart disease can be a risk factor for cardiac adverse reactions. Caution is therefore indicated when treating patients who have experienced chest pain during the treatment cycles and in patients with known heart disease. During treatment with fluorouracil, heart function should be monitored regularly. In the case of severe cardiotoxicity, treatment should be discontinued.

Encephalopathy
After the market launch, cases of encephalopathy (including hyperammonemic encephalopathy and leukoencephalopathy) that were associated with treatment with 5-fluorouracil were reported. Signs and symptoms of encephalopathy include changes in mental state, disorientation, coma or ataxia. If one of these symptoms occurs, the treatment should be stopped immediately and the serum ammonia values should be tested. In the case of elevated serum ammonia values, ammonia-lowering treatment must be initiated.

Caution is advised when administering fluorouracil to patients with impaired renal and/or hepatic function. In patients with impaired renal and/or hepatic function, there may be an increased risk of hyperammonemia and hyperammonemic encephalopathy.

Dihydropyrimidine dehydrogenase (DPD) deficiency
The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the reduction of 5-fluorouracil. The DPD activity is rate-limiting in the catabolism of 5-fluorouracil (see Section 5.2). Patients with DPD deficiency are therefore at an increased risk of fluoropyrimidine-related toxicity, such as stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Toxicity caused by DPD deficiency usually occurs during the first treatment cycle or after a dose increase.

Complete DPD deficiency
A 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 should not be treated with 5-fluorouracil (see Section 4.3).

Partial DPD deficiency
A partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partial DPD deficiency have an increased risk of serious and potentially life-threatening toxicity. In patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD gene locus) where the benefit of 5-fluorouracil outweighs the risk-taking into consideration the suitability of an alternative non-fluoropyrimidine chemotherapy regimen - it is necessary to proceed with extreme caution. Regular checks with dosage adjustments must be performed depending on toxicity. A reduced initial dose should be considered to limit this toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity measured with a specific test. A DPD deficiency must be considered a parameter that is to be taken into consideration in conjunction with other routine measures for a dose reduction. Reducing the initial dose may affect the efficacy of the treatment. If no serious toxicity is present, the following doses can be increased under close monitoring.

It was reported that the c.1905+1G>A, c.1679T>G variants led to a greater reduction in enzymatic activity than the other variants, associated with a higher risk of adverse reactions. The effect of a reduced dose on efficacy is currently uncertain. Patients who have tested negative for the above-mentioned allele may still have a high risk of serious adverse reactions.

Investigations for a DPD deficiency
It is recommended that a phenotypic and/or genotypic assessment be performed before starting treatment with 5-fluorouracil, even if there are uncertainties about the optimal test methods prior to treatment. Applicable clinical guidelines must be taken into consideration.

Genotypic characterisation of the DPD deficiency
Pre-treatment tests for rare mutations in the DPYD gene may 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 may lead to a completely missing or reduced enzymatic DPD activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity.

It is known that certain homozygous and complex heterozygous mutations in the DPYD locus (e.g., combinations of the four variants with at least one allele of c.1905+1G>A or c.1679T>G) may result in completely or almost completely absent enzymatic DPD activity.

Patients with specific heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c.2846A>T und c.1236G>A/HapB3 variants) showed an 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 approximately 1%, 1.1 % for c.2846A>T, 2.6% - 6.3% for c.1236G>A/HapB3 variants and 0.07% to 0.1 % for c.1679T>G. Genotyping on this allele is recommended to identify patients at increased risk of severe toxicities. Information on the frequency of these DPYD variants in populations other than Caucasians is limited. It is currently believed that the four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) practically do not exist in populations of African (Afro-American) or Asian origin.

Phenotypical characterisation of a DPD deficiency
For the phenotypical characterisation of the DPD deficiency, the measurement of the concentrations of the endogenous DPD substrate Uracil (U) in plasma is recommended prior to the start of treatment.

Increased uracil concentrations prior to treatment are associated with an increased risk of toxicity. Despite uncertainties regarding the uracil threshold values that define complete and partial DPD deficiency, a uracil level in the blood of ≥ 16 ng/ml and <150 ng/ml should be viewed as an indicator of partial DPD deficiency and considered an increased risk for fluoropyrimidine toxicity. A urine uracil level of ≥ 150 ng/ml should be viewed as an indicator of a complete DPD deficiency and considered a risk for life-threatening or fatal fluoropyrimidine toxicity.

Life-threatening toxicity can occur in patients with unknown DPD deficiency who were treated with 5-fluorouracil as well as patients who tested negative for specific DPYD variants, manifesting in the form of acute overdose (see Section 4.9). In the case of acute toxicity of grades 2–4, treatment must be stopped immediately. A permanent interruption should be considered based on the clinical evaluation of the start, duration and severity of the observed toxicity.

Nucleoside analogues such as brivudine, sorivudine and others
The interaction between brivudine and fluoropyrimidines is potentially fatal. Deaths have been reported from this interaction. Therefore, a waiting period of at least four weeks must be observed between treatment with brivudine (as well as sorivudine and analogues) and therapy with fluoropyrimidine-containing drugs (see Sections 4.3, 4.5 and 4.8).

Due to the possibility of the occurrence of an anaphylactic reaction, the usual anti-shock control means should be provided prior to the use of 5-fluorouracil.

Patients receiving phenytoin concomitantly with 5-fluorouracil should be examined regularly due to potentially elevated phenytoin plasma levels.

Damage to the intestinal wall requires symptomatic treatment depending on severity, for example, fluid substitution. Mild diarrhoea can be treated with antidiarrhoeal drugs. However, these are not sufficient for moderate to severe diarrhoea.

Prior to and during treatment with 5-fluorouracil, the following tests are recommended:

- daily inspection of the oral cavity and throat with regard to changes in the mucous membranes
- Blood count including differential blood count and platelets before each administration of 5-fluorouracil and every 2-3 days at the start of treatment
- Retention values at regular intervals
- Liver values at regular intervals
- Determination of uric acid levels
- Examination of stool for occult blood.

Patients must be informed about the possible occurrence of stomatitis/mucositis, diarrhoea and bleeding (especially from the gastrointestinal tract). They must be informed that they should inform the responsible physician at the first signs. Immediate discontinuation of treatment is required in case of the following symptoms: gastrointestinal reactions (stomatitis, mucositis, severe diarrhoea, severe vomiting, ulcers, bleeding), leukocytes < 3,000/µl, platelets < 80,000/µl, central (including ataxia and tremor) and cardiac adverse reactions.

Treatment may only be continued after the adverse reactions have subsided and if the patient's general condition permits it. In the case of severe gastrointestinal, cardiac or neurological toxicity symptoms, it is generally advisable not to resume treatment.

If 5-fluorouracil and oral anticoagulants are administered simultaneously, the Quick value must be monitored closely.

Special caution is indicated for high-risk patients after high-dose pelvic radiation, after therapy with alkylating agents, with extensive bone metastases and extensive liver metastases (reduced degradation) and cachectic patients.

In combination with methotrexate, methotrexate is to be applied to achieve an optimal effect up to 24 hours before 5-fluorouracil (not reversed!).

5-Fluorouracil can act mutagenically. Men who are treated with 5-fluorouracil are therefore advised not to father children during treatment and for up to 6 months after the completion of treatment, and to seek advice on sperm conservation prior to the start of treatment due to the possibility of severe disorders of spermatogenesis as a result of treatment. Women must not become pregnant during therapy with 5-fluorouracil and must take effective contraceptive measures. Genetic counselling is recommended for patients who wish to have children after treatment.

Paediatric population
Not enough research has been done on the efficacy and safety of 5-fluorouracil in children and adolescents.

4.5 Interaction with other medicinal products and other forms of interaction
Please note that the following information can also refer to recently administered drugs.

Contraindicated are combinations with:

Nucleoside analogues such as brivudine and sorivudine, amongst others
A clinically significant interaction between fluoropyrimidines such as 5-FU and brivudine was described (see also Sections 4.3, 4.4 and 4.8).

This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.

There must be an interval of at least four weeks between the end of treatment with brivudine and the start of therapy with 5-FU or other fluoropyrimidine-containing medicinal products.

All therapeutic measures that worsen the physical state of the patient or have myeloid effects (e.g., other cytostatics) may increase the toxicity of 5-fluorouracil.

Fluorouracil can intensify the toxic effect on the skin caused by radiation therapy.

Calcium folate may potentiate the effects of 5-fluorouracil. As a clinical consequence of this interaction, severe, sometimes fatal diarrhoea can occur. An accumulation of such deaths was particularly associated with an administration regimen of an i.v. bolus injection of 600 mg 5-fluorouracil per m2 body surface area once weekly in combination with calcium folinate.
In concomitant administration of phenytoin and 5-fluorouracil, there were reports of an increase in plasma concentrations of phenytoin, which led to symptoms of phenytoin intoxication.

Cimetidine, metronidazole, allopurinol and interferons can increase the plasma levels of 5-fluorouracil. This can increase the toxic effects of 5-fluorouracil.

In female patients who received diuretics of the thiazide-type in addition to cyclophosphamide, methotrexate and 5-fluorouracil, the number of granulocytes was more significantly reduced than after the same number of cytostatic cycles without thiazide.

Concomitant administration of 5-fluorouracil and warfarin may lead to prolongation of the prothrombin time. Therefore, this should be closely monitored. In individual cases, a drop in the Quick value was observed in patients who were treated with warfarin and additionally 5-fluorouracil alone or in combination with levamisole.

During concomitant treatment with 5-fluorouracil and levamisole, hepatotoxic effects (increase in alkaline phosphatase, transaminases, or bilirubin) are often observed.

In patients with breast cancer who received combination treatment with cyclophosphamides, methotrexate, 5-fluorouracil and tamoxifen, there was an increased risk of occurrence of thromboembolic events.

In the case of concomitant administration of vinorelbine and 5-fluorouracil/folinic acid, severe and potentially fatal mucositis may occur.

The assay techniques for bilirubin and 5-hydroxyindole-acetic acid in urine can result in elevated or false positive values.

Aminophenazone, phenylbutazone and sulphonamides should not be given before and during treatment.

Chlordiazepoxide, disulfiram, griseofulvin and isoniazid can intensify the effects of 5-fluorouracil.

After long-term use of 5-fluorouracil in combination with mitomycin, haemolytic-uraemic syndrome was reported.

Very rarely, the occurrence of cerebral infarction has been reported in a temporal association with a 5-fluorouracil therapy in combination with other chemotherapeutic agents (mitomycin Cor cisplatin).

General information
Cytostatics can reduce the formation of antibodies after an influenza vaccination. Cytostatics can increase the risk of serious infections after administration of live vaccines.

Incompatibilities
5-Fluorouracil may only be diluted with a physiological saline solution or a 5% glucose solution. 5-Fluorouracil must not be mixed with other substances in an infusion.

Incompatibilities were reported with the following substances:
Cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, leucovorin, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutrient solutions, vinorelbine.

4.6 Fertility, pregnancy and lactation

Pregnancy
5-Fluorouracil may be mutagenic and must not be administered during pregnancy (see section 4.3). Women of childbearing age must ensure effective contraception during treatment and up to 6 months thereafter. If there is a pregnancy during treatment, the possibility of genetic counselling must be considered.

Animal experiments showed teratogenic reactions in the foetus. 5-Fluorouracil presumably causes serious harm to the unborn child when used during pregnancy.

Breastfeeding
As it is not known whether 5-fluorouracil passes into breast milk, women who receive the product must not breastfeed. If its use is necessary during breastfeeding, weaning must take place beforehand (see Section 4.3).

Fertility
5-Fluorouracil can cause genetic harm. Men who are treated with 5-fluorouracil are, therefore, advised not to father children during as well as up to 6 months after treatment. Due to the possibility of severe spermatogenesis disorders as a result of therapy with 5-fluorouracil, a consultation regarding sperm conservation is recommended prior to treatment.

4.7 Effects on the ability to drive and use machines
5-Fluorouracil may cause nausea, vomiting, adverse reactions of the nervous system and vision changes and thus indirectly affect the ability to drive or use machines. Therefore, you should not drive or use machines during treatment with 5-fluorouracil.

4.8 Undesirable effects
The most common and most serious adverse reactions of 5-fluorouracil are bone marrow toxicity and gastrointestinal symptoms.

The evaluation of adverse reactions is based on 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) Unknown (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders
Very common: Myelosuppression (leucopenia, neutropenia, thrombocytopenia), anaemia
Common: febrile neutropenia
Very rare: Agranulocytosis, pancytopenia

Infections and parasitic disorders:
Very common: Infections
Common: Immunosuppression with increased risk of infection
Rare: Sepsis

Immune system disorders
Rare: General allergic reactions, anaphylaxis, anaphylactic shock

Endocrine disorders
Not known: Total thyroxine (T4) and total triiodothyronine (T3) in the serum can increase without elevation of the free T4 and TSH and without clinical signs of hyperthyroidism (patients remain clinically euthyroid)

Metabolism and nutritional disorders
Very common: Hyperuricaemia

Psychiatric disorders
Rare: Confusion

Nervous system disorders
Uncommon: Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal tract signs, euphoria, somnolence
Rare: Peripheral neuropathy (in combination with radiotherapy)
Very rare: Dysgeusia, (leuko-) encephalopathy with ataxia, acute cerebral syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma

Unknown: Hyperammonemic encephalopathy

Eye disorders
Uncommon: Increased lacrimation and stenosis of the tear canal, blurred vision, disorders of eye motility, inflammation of the optic nerves, double vision, reduced visual acuity, photophobia, conjunctivitis, inflammation of the eyelids, ectropion due to scar formation and fibrosis of the lacrimal glands

Cardiac disorders
Very common: Ischaemic ECG abnormalities Common: Angina pectoris-like chest pain
Uncommon: Arrhythmia, myocardial infarction, myocardial ischaemia, myocarditis, heart failure, dilative cardiomyopathy, cardiogenic shock
Very rare: Cardiac arrest, sudden cardiac death
Not known: Pericarditis

Vascular disorders
Uncommon: Hypotension
Rare: Thrombophlebitis
Unknown: Cerebral, intestinal and peripheral ischaemia, Raynaud's syndrome, thromboembolism

Respiratory, thoracic and mediastinal disorders
Very common: Bronchospasm, epistaxis

Gastrointestinal disorders
Very common: Gastrointestinal disorders (sometimes life-threatening) such as mucositis (stomatitis, pharyngitis, oesophagitis, proctitis), anorexia, (watery) diarrhoea, nausea, vomiting (see also section 4.4)
Uncommon: Dehydration, ulcers and bleeding in the gastrointestinal tract, necrotic rejection

Hepatobiliary disorders
Uncommon: Liver cell damage, stoneless cholecystitis Very rare: Liver necrosis (cases with fatal outcome)

Skin and subcutaneous tissue disorders
Very common: alopecia, palmar-plantar erythrodysesthesia syndrome (so-called "hand-foot syndrome") with dysaesthesia, redness, swelling, pain and scaling of the skin on the palms and soles of the feet
Uncommon: dermatitis, changes in the skin (dry skin, erosion/fissures, erythema, pruritic maculopapular skin rash), exanthema, urticaria, photosensitivity, hyperpigmentation of the skin, stripe-like hyperpigmentation or depigmentation near veins, nail changes (e.g., diffuse superficial blue pigmentation, hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia), onycholysis

Disorders of the reproductive system and mammary glands
Uncommon: Disorders of spermatogenesis and ovulation

General disorders and administration site complaints
Very common: delayed wound healing, exhaustion, general asthenia, fatigue, lack of drive, fever

Description of selected adverse reactions

Blood and lymphatic system disorders

Myelosuppression is one of the dose-limiting adverse reactions (see also Section 4.2). The degree of severity (NCI Grade I–IV) of myelosuppression depends on the type of administration (i.v. bolus injection or i.v. continuous infusion) and the dosage. Neutropenia occurs after each therapy cycle with an i.v. bolus injection with adequate doses (nadir: 9th–14th–(20th) day of therapy; normal values: usually after day 30).

Cardiac disorders

Cardiotoxic effects usually occur during or within a few hours after the first treatment cycle. In patients with pre-existing coronary heart disease or cardiomyopathy, there is an increased risk of cardiotoxicity.

Gastrointestinal disorders

The severity level (NCI Grade I–IV) of gastrointestinal adverse reactions depends on the dosage and method of administration. In the case of a continuous i.v. infusion, stomatitis is more likely to be the dose-limiting factor than myelosuppression.

Skin and subcutaneous tissue disorders

So-called hand-foot syndrome begins with dysaesthesia of the palms and soles of the feet, with reddening, swelling, pain and scaling of the skin in the further course. It is **very common** after continuous i.v. administration and **common** after i.v. bolus injection.

Brivudine may interact with chemotherapeutic agents of the fluoropyrimidine type. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal (see also Sections 4.3, 4.4 and 4.5).

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 e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

Symptoms of an overdose

In the event of an overdose, the symptoms listed under adverse reactions such as nausea, vomiting, diarrhoea, severe mucositis, ulcers and bleeding in the gastrointestinal tract, bone marrow depression (thrombocytopenia, leucopenia, agranulocytosis) occur at a higher rate/with greater severity.

Acute:

Psychotic reactions, somnolence, potentiation of the effects of sedating medicinal products, increased alcohol toxicity.

If sedation is necessary, diazepam i.v. may be administered in small doses (e.g., starting with 5 mg) while monitoring circulation and respiration.

Chronic:
Bone marrow depression up to agranulocytosis and critical thrombocytopenia, bleeding tendency, gastrointestinal tract ulcers, diarrhoea and hair loss.

Therapeutic measures
If symptoms of intoxication occur, administration of 5-fluorouracil should be stopped immediately. Measures for symptomatic treatment must be taken. Infusions of leukocyte or platelet concentrate, infection prophylaxis. Forced diuresis to compensate for the volume and mineral balance can be favourable. Haemodialysis is generally not necessary. Careful monitoring to detect haematological and gastrointestinal delayed complications in a timely manner.

Permanent myelosuppression must be treated under inpatient conditions. This includes, if necessary, substitution of the missing blood components and antibiotic therapy. The patient may need to be moved into an aseptic room.

Haematological monitoring is recommended up to 4 weeks after an overdose.

If treatment with 5-fluorouracil is to be continued despite cardiac adverse reactions, the administration of vasodilators is indicated to avoid spasms of the coronary arteries.

There is no known specific antidote for casirivimab and imdevimab overdose. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 9.2.1 Folic acid analogues.

The antimetabolite 5-fluorouracil represents a fluorinated pyrimidine. 5-Fluorouracil is activated enzymatically with deoxyfluorouracil monophosphate. This inhibits the activity of thymidylate synthetase and thus the synthesis of deoxythymidine monophosphate by means of complex formation. This results in a phase-specific inhibition of DNA synthesis. Furthermore, dioxyfluoronucleotides inhibit the new synthesis of pyrimidine nucleotides.

Calcium folate forms a relatively stable ternary complex with 5-fluorouracil and thymidylate synthetase, thereby prolonging the inhibitory effects of 5-fluorouracil on thymidylate synthetase. This results in potentiation of the cytotoxic effects of 5-fluorouracil.

5-Fluorouracil acts in the cell cycle in a phase-specific manner, especially in the S-phase. The effect of the substance is particularly pronounced in rapidly proliferating tissue (bone marrow, skin and mucous membranes).

5.2 Pharmacokinetic properties
5-Fluorouracil is also catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) into the significantly less toxic form of dihydro-5-fluorouracil (FUH2). The enzyme dihydropyrimidinase splits the pyrimidine ring into 5-fluoroureidopropionic acid (FUPA). Finally, the ß-ureidopropionase splits FUPA into α-fluoro-ß-alanine (FBAL) that is excreted

with the urine. The activity of dihydropyrimidinase dehydrogenase (DPD) determines the rate. A deficiency of DPD can lead to increased toxicity of 5-fluorouracil (see sections 4.3 and 4.4).

5-Fluorouracil is only incompletely absorbed via the oral route (0-80%).

The substance has a distribution of 0.12 l/kg BW (after 15 mg/kg BW i.v.) and is particularly recovered in rapidly proliferating tissue such as bone marrow, intestinal mucous membranes and neoplasias; 5- fluorouracil passes the blood-brain barrier.

Metabolism takes place in the liver and is similar to that of uracil. 5-fluorouracil undergoes rapid enzymatic conversion into the active metabolite dihydro-5-fluorouracil, which has a significantly longer half-life than 5-fluorouracil. Other non-toxic degradation products include carbon dioxide and urea.

The plasma half-life (alpha phase) is between 8 and 22 minutes. The elimination half-life (beta phase) reaches approximately 20 hours due to the active metabolites in the tissue and is dose-dependent.

5-fluorouracil (60-80%) is primarily exhaled as carbon dioxide via the lungs. Secondarily, 5-fluorouracil is excreted unchanged via the renal route (approx. 7-20%); approx. 90% within the first hour. Renal clearance is about 170-180 ml/min. The substance is excreted slowly if renal function is impaired.

In the cerebrospinal fluid, the maximum concentration is reached after approximately 1.5 - 2 hours and equals approximately 50% of the plasma concentration.

Kinetics in special clinical situations: despite the low renally eliminated portion (approx. 15%), due to impairment of bone marrow function with azotaemia (as a consequence of renal insufficiency) and any interference with platelets, a dosage adjustment that corresponds to the degree of renal insufficiency and the reaction of the individual patient is indicated. If liver function is impaired, a dosage adjustment should also be considered.

5.3 Preclinical safety data

Toxicity

The cell division inhibitory effect of 5-fluorouracil primarily affects rapidly proliferating tissue (both tumour-producing and healthy tissue). Accordingly, toxicities are displayed particularly in the bone marrow, with leucopenia, thrombocytopenia, gastrointestinal tract bleeding, and secondarily in the form of infections.

Reproductive toxicity/mutagenicity/carcinogenicity

In various *in vitro* cultures, fluorouracil shows mutagenic potential (various *Salmonella typhimurium* strains, micronucleus test in mice; in high concentrations, it causes chromosomal strand breaks in hamster fibroblasts). *In vivo*, male rats showed chromosomal aberrations and changes in spermatogenesis ranging to infertility. In female rats, fluorouracil reduced fertility and induced chromosomal aberrations in the embryos. Lesser effects were observed in rabbits.

Antimetabolites showed carcinogenic properties in animal experiments. However, the risk of developing secondary tumours appears to be lower in humans than with alkylating substances.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium hydroxide
Water for injection

6.2 Incompatibilities
5-Fluorouracil must only be diluted with a saline or 5% glucose solution. 5-Fluorouracil must not be mixed with other substances in an infusion.

5-Fluorouracil must not be diluted with strongly buffered solutions with a pH < 8 since 5-fluorouracil would precipitate in this environment. Do not mix with other chemotherapeutic solutions.

Incompatibilities were reported with the following active substances:
Fluorouracil is incompatible with folinic acid, carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutrition, vinorelbine and other anthracyclines.

Calcium folinate
Calcium folinate must not be mixed with 5-fluorouracil in the same infusion, as a precipitate may form. It has been shown that 5-fluorouracil 50 mg/ml is incompatible with calcium folinate 20 mg/ml with or without dextrose 5% in water when it is mixed in different quantities and stored in containers made of polyvinyl chloride at 4°C, 23°C or 32°C.

5-Fluorouracil solution for injection/infusion must not be mixed with other medicines, including oxaliplatin or irinotecan.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 25°C. Do not refrigerate or freeze.

For single use only.
Only use clear and colourless to pale yellow solutions.

If precipitations occur due to storage at low temperatures, they can be dissolved by carefully heating to 60°C and shaking. Allow to cool before administration.

Shelf life after dilution
Dilution can be performed with sodium chloride 0.9% solution or 5% glucose solution. Stability data for concentrations of 0.35 mg/ml and 15 mg/ml have shown that the maximum storage time of the ready-to-use 5-fluorouracil solution for infusion is 28 days. This storage time refers both to storage in the refrigerator (2–8°C), including protection from light, as well as storage at room temperature (20–25°C) with or without protection from light. The chemical and physical stability of the ready-to-use infusion preparation was proven to be over 28 days, but the ready-to-use solution must be used immediately from a microbiological perspective. If it is not used immediately, the storage conditions of the ready-to-use infusion preparation prior to administration become the responsibility of the user and normally do not

exceed 24 hours at 2–8°C, unless dilution has taken place under controlled and validated aseptic conditions.

6.5 Nature and contents of the container
A USP type I amber glass vial closed with a rubber stopper.

5-Flurouracil Sandoz 500 mg/10 mL
Fill volume: 10 mL.
Pack size: 1 vial per carton.

5-Flurouracil Sandoz 1 g/20 mL
Fill volume: 20 mL.
Pack size: 1 vial per carton.

6.6 Special precautions for disposal and other handling
Due to possible mutagenic and carcinogenic effects, increased safety measures apply to hospital staff and physicians. During the handling of 5-fluorouracil, any contact with the skin and mucous membranes must be avoided, otherwise, immediate cleaning with water and soap is necessary. If the eyes are contaminated, they must be immediately rinsed with water and medical attention must be sought. All precautions must be taken to enable absolutely aseptic work. The use of a working area with laminar flow is recommended. Protective clothing must be worn while handling 5-fluorouracil.

Pregnant personnel must not work with fluorouracil. Inactivation:
* 700°C
* Dilute sodium hypochlorite (Liquor Natrii hypochlorosi) with 10 parts of water.
* Concentrated NaOH over several hours.

The finished solution should be used immediately after preparation. Precipitates resulting from storage at low temperatures can be dissolved by shaking and cautious heating to 60°C – allow to cool before application.

The literature describes a loss of efficacy by adsorption of 5-fluorouracil in the glass infusion container.

Handling and disposal specifications specified for cytostatic agents must be observed. Unused medicines or waste materials should be disposed of according to national regulations.

7. APPLICANT
Sandoz SA (Pty) Ltd
Waterfall 5-lr, Magwa Crescent West
Waterfall City, Jukskei View 2090
Gauteng
South Africa

8. MANUFACTURERS
Fareva Unterach GmbH
Mondseestraße 11
4866 Unterach

Austria

9. REGISTRATION DETAILS

5-Flurouracil Sandoz 500 mg/10 mL
Zimbabwe registration number: 2023/9.2.1/6479
Zimbabwe category for distribution: Prescription Preparations (P.P.)

5-Flurouracil Sandoz 1 g/20 mL
Zimbabwe registration number: 2023/9.2.1/6480
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT

November 2023