Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

IMPORTANT INFORMATION
FOR HEALTHCARE PROFESSIONALS AND PATIENTS
CAUTION IN USE LETTER

11 May 2022

Re: Supply shortage of Fluorouracil 25 mg/ml Solution for Injection or Infusion (PA 0822/223/001) and availability of unlicensed Fluorouracil alternative from France

To Healthcare Professionals

(Electronic version of this letter is also available on the HPRA website: https://www.hpra.ie/homepage/medicines/medicines-information/medicines-shortages)

I am writing to you in connection with the supply of the above and following referenced product:

- Fluorouracil 25 mg/ml Solution for Injection or Infusion (PA 0822/223/001)

Due to supply disruptions, Pfizer Healthcare Ireland are unable to supply Irish licensed packs of Fluorouracil 25 mg/ml Solution for Injection or Infusion (PA 0822/223/001) to the Irish market. To mitigate an out of stock of Fluorouracil 25 mg/ml (pack size 2.5g/100ml) Pfizer Healthcare Ireland have now obtained supply of an alternative unlicensed product from France – **FLUOROURACILE PFIZER 50 mg/ml, solution à diluer pour perfusion (FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion, pack size 1 g/20 ml) (Batch number: N1C15A; Expiry date: 28.02.2023)** – through the exempt medicinal product framework. **Note: difference in product strengths between Irish and French products.**

This unlicensed product, **FLUOROURACILE PFIZER 50 mg/mL,** concentrate for solution for infusion is approved in France and will be supplied on a temporary basis in response to a bona fide order for this exempt presentation. HCPs should assess the below tabular formatted differences in labelling to Fluorouracil 25 mg/ml Solution for Injection or Infusion prior to any exempt presentation order request.

A summary of the key points are as follows:

- To help mitigate the national shortfall in supply against demand, the Health Products Regulatory Authority (HPRA) have been notified of the importation of Pfizer stock of **FLUOROURACILE PFIZER 50 mg/mL**, concentrate for solution for infusion, pack size 1 g/20 ml from France.

- The constituents/excipients of the Irish and French formulations are; Fluorouracil, sodium hydroxide and water for injections, however, please note the different concentration/total dose (Irish Fluorouracil: each vial contains **2.5 g/100 ml**; French Fluorouracil: each vial contains **1 g/20 ml**).

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

- **FLUOROURACILE PFIZER 50 mg/mL**, concentrate for solution for infusion is considered an unlicensed product in Ireland. Please see the table below highlighting the differences in the Irish licenced product and French licenced product.

- **The expiry for FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion is: 28.02.2023**

Please find a copy of the French Patient Information Leaflet (PIL) in English appended to this CIU letter for your information. Please remove and discard the Patient Information Leaflet in French.

For further details on the Irish licensed product please refer to the approved Irish Summary of Product Characteristics (SPC) and PIL, which are available on the HPRA website: www.hpra.ie

DIFFERENCES IN THE FRENCH AND IRISH PRESENTATIONS:

For your awareness, the key differences between **Fluorouracil 25 mg/ml Solution for Injection or Infusion** and **FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion**, as listed in the Summary of Product Characteristics, are highlighted in the table below.

PRODUCT NAME	**FLUOROURACILE PFIZER 50 mg/ml, solution à diluer pour perfusion** (FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion)	**Fluorouracil 25 mg/ml Solution for Injection or Infusion**
PRODUCT STRENGTH / DOSE	**50 mg/ml** **Each vial contains 1 g/20 ml**	**25 mg/ ml** **Each vial contains 2.5 g/100ml**
MARKETING AUTHORISATION HOLDER	**PFIZER HOLDING FRANCE** 23-25 AVENUE DU DOCTEUR LANNELONGUE 75014 PARIS	Pfizer Healthcare Ireland 9 Riverwalk National Digital Park Citywest Business Campus Dublin 24 Ireland
LICENSED INDICATIONS	• Advanced gastrointestinal adenocarcinomas. • Colorectal cancers after resection in adjuvant situations. • Breast adenocarcinomas after locoregional treatment or for recurrences. • Ovarian adenocarcinomas. • Squamous cell carcinomas of the upper airways and oesophagus.	Fluorouracil may be used alone or in combination, for its palliative action in the management of common malignancies particularly cancer of the colon and breast.
DOSAGE & ADMINISTRATION	**Conditions of use** The use of fluorouracil should be confined to units specialized in the	Posology **Adults:**

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	administration of cytotoxic chemotherapy and fluorouracil should be administered under supervision of a physician qualified in the use of cancer chemotherapeutic agents (see sections 4.4 and 6.6). A blood count should be taken regularly during the initial phase, then every week or every two weeks during the maintenance period (see section 4.4). In patients with a history of heart disease, alcohol use and/or smoking, intensive and continuous cardiac monitoring should be maintained over the first three courses of 5 FU, during continuous IV infusion (see section 4.4). **Posology** • As monotherapy: The average dose is 400 to 600 mg/m²/day, 3 to 6 days per month, administered by IV infusion over approximately one hour. • In combination with other cytotoxic agents: 300 to 600 mg/m2/day, 2 to 5 days per cycle every 3 to 4 weeks. *More rarely*: FLUOROURACILE PFIZER 50 mg/ml concentrate for solution for infusion may be administered by slow hepatic intra-arterial infusion (over 4 to 6 hours) at a dose of 600 mg/m² weekly. It is sometimes administered by continuous intravenous infusion at a dose of 700 mg to 1 g/m² over 3 to 5 consecutive days. These methods of administration should be restricted to specialized services. In the majority of indications, the dose of 1 g/m² per injection should not be exceeded. The dose should be reduced two- or three-fold in the following cases: • surgery within 30 days prior to	The following regimen have been recommended for use as a single agent: **Initial Treatment:** This may be in the form of an infusion or an injection, the former usually being preferred because of lesser toxicity. **Intravenous Infusion:** 15 mg/kg bodyweight but not more than 1 g per infusion diluted in 300 – 500 ml of 5% glucose or 0.9% sodium chloride injection given over 4 hours. Alternatively the daily dose may be infused over 30 - 60 minutes or may be given as a continuous infusion over 24 hours. The infusion may be repeated daily until there is evidence of toxicity or a total dose of 12 – 15 g has been reached. **Intravenous Injection:** 12 mg/kg bodyweight may be given daily for 3 days and then, if there is no evidence of toxicity, 6 mg/kg on alternate days for 3 further doses. An alternative regimen is 15 mg/kg as a single intravenous injection once a week throughout the course. **Intra-arterial Infusion:** 5 - 7.5 mg/kg bodyweight daily may be given by 24 hour continuous intra-arterial infusion. **Maintenance Therapy:** An initial intensive course may be followed by maintenance therapy providing there are no significant toxic effects. In all instances, toxic side effects must disappear before maintenance therapy is started. The initial course of fluorouracil can be repeated after an interval of 4 to 6 weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5 – 15 mg/kg bodyweight at weekly intervals. This sequence constitutes a course of therapy. Some patients have received up to 30 g at a maximum rate of 1 g daily.

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

treatment,
- severely impaired liver function,
- when haematopoietic disorders are manifested by granulocytopoenia with WBC counts from 2,000 to 3,000 per mm3 or thrombocytopoenia with platelet counts below 100,000 per mm3.

Dihydropyrimidine dehydrogenase (DPD) deficiency must be considered as a parameter to be taken into account, in association with other routine dose reduction measures. A reduced starting dose may be proposed in patients with partial DPD deficiency. An initial reduction in the dose may affect the efficacy of treatment. In the absence of serious toxicities, the following doses may be increased, under careful monitoring (see section 4.4).

Therapeutic drug monitoring (TDM) of 5-fluorouracil

TDM of 5-Fluorouracil may improve the clinical prognosis in patients receiving continuous 5-fluorouracil infusions, by reducing undesirable effects and improving efficacy. The AUC is assumed to be between 20 and 30 mgx h/L (see section 4.4).

Dose adjustments during treatment

General considerations

The need to adjust the dose or discontinue treatment depends on the appearance of undesirable effects.

Reintroduction of treatment may be considered, depending on the biological and clinical parameters.

During the infusion

The occurrence of cardiac manifestations (for example chest pain) during administration requires immediate discontinuation of the continuous infusion of fluorouracil. In this case, reintroduction must not be considered (see section 4.4).

Haematology

A more recent alternative method is to give 15 mg/kg IV once a week throughout the course of treatment. This obviates the need for an initial period of daily administration.

In Combination with Irradiation

Irradiation combined with 5-FU has been found to be useful in the treatment of certain types of metastatic lesions in the lungs and for the relief of pain caused by recurrent, inoperable growth. The standard dose of 5-FU should be used.

Dose reduction in certain situations

The initial dose should be reduced by one-third to one half in patients with any of the following:
1.Cachexia.
2.Major surgery within preceding 30 days.
3.Reduced bone marrow function.

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

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

4.Impaired hepatic or renal function.

If plasma bilirubin concentration is >5 mg/dl, treatment with fluorouracil should be discontinued. If the patient's hepatic or renal function is impaired, the recommended dose can be reduced by 30 to 50% (see sections 4.4 and 5.2).

Paediatric Population

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

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	Discontinuation of treatment should be considered in the event of haematological toxicity, such as granulopenia below 2,000 white blood cells per mm3 or thrombocytopenia below 80,000 platelets per mm3 (see section 4.4). *Hepatic and/or renal impairment* Fluorouracil should be used with caution in patients with hepatic and/or renal impairment, especially due to an increased risk of hyperammonaemia and hyperammonaemic encephalopathy. A dose reduction may be considered in these patients (see section 4.4). *Stomatitis and/or diarrhoea* The occurrence of stomatitis, and especially of diarrhoea, requires discontinuation of treatment until the symptoms disappear. This also applies to the formation of gastrointestinal ulceration or the occurrence of haemorrhage at any location (see section 4.4). *Encephalopathy* Treatment must be discontinued immediately in case of encephalopathy (see section 4.4). **Method of administration** Intravenous route. Exceptionally, by slow hepatic intra-arterial infusion. If extravasation occurs, administration should be discontinued immediately. For instructions on dilution of the medicinal product before administration, see section 6.6. Do not administer by intramuscular route.	**Elderly:** Fluorouracil should be used in the elderly with similar considerations as in younger adults, notwithstanding that the incidence of concomitant medical illness is higher in the former group. Method of administration Selection of an appropriate dose and treatment regime depends upon the condition of the patient, the type of carcinoma being treated and whether fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with the patient's actual bodyweight unless there is obesity, oedema or some form of abnormal fluid retention such as ascites. Ideal weight is used as the basis for calculation in such cases. Fluorouracil may be used in combination with other cytotoxic chemotherapeutic agents; however, fluorouracil injection should not be mixed directly in the same container with other chemotherapeutic agents or intravenous additives. Fluorouracil Injection BP can be given by intravenous injection or infusion or intra-arterial regional perfusion. Fluorouracil is often administered concomitantly with calcium folinate (folinic acid) which may potentiate the therapeutic effects of fluorouracil. Therefore, the toxicity of fluorouracil, especially GI and hematologic, may be increased. Careful monitoring should be observed and the dose of fluorouracil may be decreased based on current guidelines.
WARNINGS	Treatment will be discontinued if there is granulocytopoenia below 2000 white blood cells per mm3 or thrombocytopoenia with a platelet count below 80,000 per mm3 (see	All patients should be admitted to hospital for initial treatment. Fluorouracil has a narrow margin of safety and is a highly toxic drug. If the following adverse effects

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	section 4.2). **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. **Risk related to concomitant use** Brivudine must not be administered concomitantly with fluorouracil. Fatal cases have been reported following this drug-drug interaction. A minimum period of 4 weeks must be observed between the end of treatment with brivudine the start of treatment with fluorouracil Treatment with brivudine can be started 24 hours after the last dose of fluorouracil (see sections 4.3 and 4.5). In the event of accidental administration of brivudine to a patient who has received fluorouracil, all treatments must be discontinued and effective measures taken to reduce the toxicity of fluorouracil. Immediate hospitalisation is recommended. All measures should be taken to prevent systemic infections and dehydration. **Precautions for use** Blood counts should be checked regularly during the initial phase and then every week or every two weeks during maintenance. Patients with cardiac history or alcohol and/or tobacco use should undergo intensive, continuous cardiac monitoring during the first 3 cycles of 5-FU, during a continuous IV infusion (see section 4.2). **Excipient**	occur, discontinuation of the therapy should be considered: leukopenia, thrombocytopenia, stomatitis, intractable vomiting, diarrhea, melena, gastrointestinal ulceration and bleeding, or hemorrhage from any site. Haematological effects Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C.) count commonly being observed between the 7th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day. Daily monitoring of platelet and W.B.C. count is recommended and treatment should be stopped if platelets fall below 100,000 per mm^3 or the W.B.C. count falls below 3,500 per mm^3. If the total count is less than 2000 per mm^3, and especially if there is granulocytopenia, it is recommended that the patient be placed in protective isolation in the hospital and treated with appropriate measures to prevent systemic infection. Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to, leukopenia, granulocytopenia, pancytopenia and thrombocytopenia). Clinical consequences of severe myelosuppresion 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. Loss of appetite, nausea and vomiting are common adverse effects, which generally occur during the first week of therapy. These adverse effects can often be alleviated by antiemetics, and generally subside within 2 to 3 days. Radiotherapy Fluorouracil treatment may potentiate necrosis caused by radiation. Special risk patients Particular care should be taken in the treatment of elderly or debilitated patients, as these patients may be at increased risk of severe toxicity.

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	This medicinal product contains between 8.74 and 9.54 mg sodium per mL. For a maximum daily dose of 600 mg/m^2 and for an average body surface area of 1.8 m^2, this medicinal product contains between 188.8 and 206 mg of sodium, equivalent to between 9.45% and 10.3% of the WHO recommended maximum daily intake of 2 g of sodium for an adult.	<u>Immunosuppressant effects</u> Vaccination with a live vaccine should be avoided in patients receiving 5-fluorouracil due to the potential for serious or fatal infections. Contact should be avoid with people who have recently been treated with polio virus vaccine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. <u>Hand-foot syndrome</u> The administration of fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. Continuous-infusion fluorouracil may increase the incidence and severity of palmar-plantar erythrodysesthesia. This syndrome has been characterized as a tingling sensation of hands and feet, which may progress over the next few days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Supplementation of chemotherapy with oral pyridoxine has been reported to prevent or resolve such symptoms. <u>Combination of 5-fluorouracil and folinic acid</u> The toxicity profile of 5-fluorouracil may be enhanced or shifted by folinic acid. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. When 5-fluorouracil and folinic acid are used in combination, the fluorouracil dosage must be reduced more in cases of toxicity than when fluorouracil is used alone. Toxicities observed in patients treated with the combination are qualitatively similar to those observed in patients treated with 5-fluorouracil alone. <u>Excipient information</u> The 100ml vial contains 401 mg of sodium in each vial, equivalent to 20% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
CONTRAINDICATIONS	• In combination with live attenuated vaccines (against yellow fever, chickenpox, herpes zoster, measles, mumps rubella, tuberculosis, rotavirus and influenza) and for the 6 months following the discontinuation of	• Are seriously debilitated • Have serious liver impairment • Have been treated with brivudine, sorivudine or their chemically related analogues,which are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	chemotherapy (see section 4.5), • Patients who have received treatment with brivudine within four weeks before treatment with 5-fluorouracil, and patients who require treatment with brivudine within four weeks after treatment with 5-fluorouracil, due to a potentially fatal interaction (see section 4.5).	(DPD) (see sections 4.4 and 4.5) . Fluorouracil must not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues • Fluorouracil (5-FU) must not be given to patients homozygotic for dihydropyrimidine dehydrogenase (DPD) • Are pregnant Fluorouracil should not be used in the management of non-malignant disease
INTERACTIONS	**Contraindicated combinations** **Live attenuated vaccines (against yellow fever, chickenpox, herpes zoster, measles, mumps rubella, tuberculosis, rotavirus and influenza)** Risk of fatal generalized vaccine disease. CONTRAINDICATION and for the 6 months following discontinuation of chemotherapy. **Brivudine** A clinically significant drug interaction between brivudineand fluoropyrimidines (for example capecitabine, 5-Fluorouracil, tegafur) has been described. This interaction arises as a result of the inhibition of dihydro-pyrimidine dehydrogenase by brivudine. This interaction, which can cause increased fluoropyrimidine toxicity, is potentially fatal. Brivudine should therefore not be administered at the same time as fluorouracil (see sections 4.3 and 4.4). A minimum period of 4 weeks should be observed between the end of treatment with brivudine and the start of treatment with fluorouracil. Treatment with brivudine can be started 24 hours after the last dose of fluorouracil. **Inadvisable combinations (see section 4.4)** **Vitamin K antagonist** Large increase of the vitamin K antagonist effect and of the risk of	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). In the case of accidental administration of nucleoside analogues that inhibit DPD activity to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalization is recommended. Cytotoxic agents Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, folinic acid interferon alfa and allopurinol. In patients receiving cyclophosphamide, Methotrexate and 5-fluorouracil, addition of thiazide diuretics resulted in a more pronounced decrease of the number of granulocytes when compared to patients not receiving thiazides. In patients with breast cancer, combination therapy with cyclophosphamide, methotrexate, 5-fluorouracil and tamoxifen has been reported to increase the risk of thromboembolic events. Serious, potentially life-threatening mucositis may occur following co-administration of vinorelbine and 5-fluorouracil/folinic acid.

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	bleeding. If it cannot be avoided, more frequent monitoring of the INR. Dosage adjustment of the vitamin K antagonist during treatment by the cytotoxic and 8 days after its discontinuation. **Olaparib** Risk of increased cytotoxic myelosuppressive effect. **Phenytoin (and by extrapolation fosphenytoin)** Risk of seizures due to decreased gastrointestinal absorption of phenytoin caused by the cytotoxic medicine or loss of efficacy of the cytotoxic medicine due to an increase in its hepatic metabolism induced by phenytoin or fosphenytoin (see Section 4.4). **Combinations to take into consideration** **Flucytosine** Risk of increased hematological toxicity. **Immunosuppressants** Profound immunodepression, with risk of lymphoproliferative syndrome. **Folinic acid** Potentiation of both the cytostatic and undesirable effects of fluorouracil. **Interferon-alpha** Increased gastrointestinal toxicity of fluorouracil. **Metronidazole** Increased fluorouracil toxicity due to decreased clearance. **Ornidazole** Increase fluorouracil toxicity due to decreased clearance.	In combination with other myelosuppressive substances, dosage adjustment is necessary. Concomitant or previous radiation therapy may require dosage reduction. The cardiotoxicity of anthracyclines may be increased. Increased incidence of cerebral infarction has been reported in oropharyngeal cancer patients treated with fluorouracil and cisplatin. Calcium folinate (Folinic acid) Folinic acid enhances the binding of fluorouracil to thymidylate synthase. Both the efficacy and toxicity of 5-fluorouracil may be increased when 5-fluorouracil is used in combination with folinic acid (see section 4.2). Side effects may be more pronounced and severe diarrhoea may occur. Life-threatening diarrhoeas have been observed if 600 mg/m² of fluorouracil (i.v. bolus once weekly) is given together with folinic acid. Phenytoin The level of phenytoin should be regularly monitored in patients taking fluorouracil and the phenytoin dosage may need to be reduced. Toxicity associated with elevated phenytoin plasma concentrations have been reported during concomitant use of phenytoin with fluorouracil or its analogues. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by fluorouracil (see section 4.4). Warfarin Marked elevations of prothrombin time and INR have been reported in a few patients stabilised on Warfarin therapy following initiation of fluorouracil regimes. Adequate anticoagulant response to warfarin and other coumarin-derivative therapy should be monitored regularly in patients taking fluorouracil. Fluorouracil should be avoided in combination with clozapine due to increased risk of agranulocytosis. Cimetidine, metronidazole and interferon may increase the plasma level of 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil. Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy (see section 4.2).

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

<table>
<tr>
<td></td>
<td></td>
<td>Hepatotoxicity (increase in alkaline phosphatases, transaminases or bilirubin) has been observed commonly in patients receiving 5-fluorouracil in combination with levamisol.

Vaccination with live vaccines should be avoided in immunocompromised patients.

<u>Laboratory values</u>
Fluorouracil treatment may interfere with some laboratory tests. Increases in total serum thyroxine concentration (due to increased binding to globulin) have been reported.</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>
<table>
<tr><td colspan="2">Infections and infestations:</td></tr>
<tr><td>Very common</td><td>Infections</td></tr>
<tr><td>Common</td><td>Septicaemia</td></tr>
<tr><td>Not known</td><td>Septic shock, Sepsis, Neutropoenia, Pneumonia, Secondary infection of urinary tract, Device-related infection, Cellulitis, Pharyngitis</td></tr>
<tr><td colspan="2">Blood and lymphatic system disorders:</td></tr>
<tr><td>Very common</td><td>Bone marrow failure, Leukopoenia, Thrombocytopoenia</td></tr>
<tr><td>Common</td><td>Febrile neutropenia</td></tr>
<tr><td>Rare</td><td>Anaemia</td></tr>
<tr><td>Not known</td><td>Granulocytopoenia, Pancytopoenia</td></tr>
<tr><td colspan="2">Immune system disorders:</td></tr>
<tr><td>Not known</td><td>Anaphylactic reaction, Hypersensitivity</td></tr>
<tr><td colspan="2">Metabolism and nutrition disorders:</td></tr>
<tr><td>Not known</td><td>Tumor lysis syndrome, Lactic acidosis, Dehydration, Reduced appetite</td></tr>
<tr><td colspan="2">Psychiatric disorders:</td></tr>
</table>
</td>
<td>
<table>
<tr><td colspan="2">Infections and infestations:</td></tr>
<tr><td>Very common</td><td>Infections, Pharyngitis</td></tr>
<tr><td>Common</td><td>Sepsis</td></tr>
<tr><td>Frequency not known</td><td>Septic shock, Neutropenic sepsis, Pneumonia, Superinfection, Urinary tract infection, Device related infection, Cellulitis</td></tr>
<tr><td colspan="2">Blood and lymphatic system disorders:</td></tr>
<tr><td>Very common</td><td>Myelosuppression[a], Neutropenia, Thrombocytopenia, Leukopenia, Agranulocytosis, Anaemia and Pancytopenia</td></tr>
<tr><td>Common</td><td>Febrile neutropenia</td></tr>
<tr><td>Frequency not known</td><td>Granulocytopenia</td></tr>
<tr><td colspan="2">Immune system disorders:</td></tr>
<tr><td>Very common</td><td>Bronchospasm, Immunosuppression with an increased risk of infection</td></tr>
<tr><td>Rare</td><td>Generalized allergic reactions, Anaphylaxis, Anaphylactic shock</td></tr>
<tr><td>Frequency not known</td><td>Hypersensitivity</td></tr>
<tr><td colspan="2">Endocrine disorders:</td></tr>
<tr><td>Rare</td><td>Increase of T4 (total thyroxine). increase of T3 (total triiodothyronine)</td></tr>
<tr><td colspan="2">Metabolism and nutrition disorders:</td></tr>
<tr><td>Very common</td><td>Hyperuricemia</td></tr>
<tr><td>Uncommon</td><td>Dehydration</td></tr>
</table>
</td>
</tr>
</table>

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

Not known	Confused state, Disorientation, Euphoric mood
Nervous system disorders:	
Not known	Cerebellar syndrome, Leukoencephalopathy[a], Cerebellar ataxia, Headache, Nystagmus, Hyperammonaemic Encephalopathy, Posterior reversible encephalopathy syndrome (PRES)
Eye disorders:	
Not known	Photophobia, Visual disturbances, Increased tear production, Acquired dacryostenosis
Cardiac disorders:	
Common	Myocardial infarction, Angina pectoris[b]
Very rare	Cardiac arrest
Frequency not known	Cardiac shock, Cardiac failure, Stress cardiomyopathy (takotsubo syndrome), Cardiomyopathy, Myocarditis, Pericarditis,
Vascular disorders:	
Not known	Haemorrhage, Thrombophlebitis
Gastrointestinal disorders:	
Very common	Diarrhoea, Stomatitis, Inflammation of the mucus membrane, Vomiting, Nausea
Not known	Gastrointestinal bleeding, Gastrointestinal ulcer, Oesophagitis, Melena, Pneumatosis intestinalis
Skin and subcutaneous tissue disorders:	

Frequency not known	Decreased appetite
Psychiatric disorders:	
Uncommon	Euphoric mood
Rare	Confusional state
Frequency not known	Disorientation
Nervous system disorders:	
Uncommon	Nystagmus, Headache, Dizziness, Symptoms of Parkinson's disease, Pyramidal signs, Somnolence
Very rare	Leukoencephalopathy
Frequency not known	Peripheral neuropathy, Epilepsy, Hyperammonaemic encephalopathy, Cerebellar syndrome
Eye disorders:	
Uncommon	Excessive lacrimation, Blurred vision, Eye movement disturbance, Optic neuritis, Diplopia, Decrease in visual acuity, Photophobia, Conjunctivitis, Blepharitis, Ectropion, Dacryostenosis
Cardiac disorders:	
Very common	Ischemic ECG abnormalities
Common	Myocardial infarction, Angina pectoris-like chest pain
Uncommon	Arrhythmia, Myocardial ischemia, Myocarditis, Cardiac insufficiency, Dilated cardiomyopathy, Cardiac shock
Very rare	Cardiac arrest, Sudden cardiac death[b]
Frequency not known	Intracardiac thrombus, Cardiac failure, Pericarditis
Vascular disorders:	
Rare	Cerebral, Intestinal and peripheral ischemia, Raynaud's syndrome, Thromboembolism, Thrombophlebitis/ Vein tracking
Uncommon	Hypotension
Frequency not known	Haemorrhage

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

Very common	Alopecia[c]
Common	Palmar-plantar erythridysesthesia syndrome[d]
Not known	Cutaneous lupus erythematosus, Dermatitis[e], Photosensitisation reaction, Skin hyperpigmentation, Cracked skin, Skin dryness, Nail disorders[f], Urticaria, Rash
General disorders and administration site conditions:	
Not known	Pyrexia, Chest pain, Injection site reaction
Investigations:	
Common	Changes to electrocardiogram

[a] including ataxia, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma
[b] Observed in patients receiving high doses of leucovorin (LV) and 5-fluorouracil (5FU) bolus and continuous infusion
[c] Reversible
[d] Observed in patients receiving 5FU and LV bolus
[e] Often manifests as maculopapular rash, with itching in the extremities
[f] For example, complete or partial detachment of the nails

Gastrointestinal disorders:	
Very common	Mucositis (Stomatitis, Oesophagitis, Proctitis), Anorexia, Watery diarrhoea, Nausea, Vomiting
Uncommon	Gastrointestinal ulceration and bleeding, Sloughing
Frequency not known	Melaena
Hepatobiliary disorders:	
Uncommon	Liver cell damage
Very rare	Liver necrosis (cases with fatal outcome), Biliary sclerosis, Cholecystitis
Skin and subcutaneous tissue disorders:	
Very common	Alopecia. Palmar-plantar erythrodysaesthesia syndrome (Hand-foot syndrome)[c]
Uncommon	Dermatitis, Skin alterations (e.g. Dry skin, Fissure erosion, Erythema, Pruritic maculopapular rash), Exanthema, Urticaria, Photosensitivity, Hyperpigmentation of the skin, Streaky hyperpigmentation or depigmentation near the veins. Changes in the nails (e.g. Diffuse superficial blue pigmentation, Hyperpigmentation, Nail dystrophy, Pain and thickening of the nail bed, Paronychia) and Onycholysis
Musculoskeletal and connective tissue disorders:	
Frequency not known	Drug-induced lupus erythematosus
Reproductive system and breast disorder:	
Uncommon	Spermatogenesis and Ovulation disorder
General disorders and administration site conditions:	
Very Common	Delayed wound healing, Epistaxis, Fatigue, General

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

		<table><tr><td></td><td>weakness, Tiredness, Lack of energy</td></tr><tr><td>Frequency not known</td><td>Pyrexia, Chest pain, Injection site reaction</td></tr><tr><td colspan="2">Investigations:</td></tr><tr><td>Common</td><td>Electrocardiogram change</td></tr></table> [a] Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days. [b] Cardiotoxic adverse events mostly occur during or within hours following the first treatment cycle. There is an increased risk of cardiotoxicity in patients with previous coronary heart disease or cardiomyopathy. [c] hand-foot syndrome has been noted with protracted and high dose continuous infusion. The syndrome begins with dysaesthesia of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot.
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 national reporting system: French National Agency for Medicines and Health Products Safety (ANSM) and the French Regional Pharmacovigilance Centres network - website: www.signalement-sante.gouv.fr.	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 HPRA Pharmacovigilance. Website: www.hpra.ie.
PRIMARY CONTAINER & CONTENTS OF THE PACK	20 mL in vial (glass) with closure (bromobutyl); box of 6.	Fluorouracil 25 mg/ml Injection is presented in Type I conventional clear glass vials with rubber stoppers and Type I clear ONCO-TAIN® vials with rubber stoppers. Fluorouracil 25 mg/ml Injection is available in the following pack sizes: 10 ml, 20 ml and 100 ml, and in packs of 1, 5 and 10 vials. Not all pack sizes may be marketed.
STORAGE	Store at a temperature between +15°C and +25°C.	Do not store above 25°C. Do not refrigerate or freeze. Keep the vials in the outer carton in order to protect from light.

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

	This product is sensitive to the light; store the immediate container in the outer package. Exposure to temperatures below +15°C may cause the appearance of particles, a phenomenon reversible simply by heating the vial.	
DILUTION	Ensure the compatibility of the 5-fluorouracil before mixing or association with any other products. **Dilutions** 15 mL of solution for injection may be mixed with 250 mL of the following solutions: Sodium chloride 0.9%, Glucose 5%, Glucose 10%, Glucose 2.5% + sodium chloride 0.45%, Ringer solution, Hartmann solution.	Diluents Fluorouracil Injection B.P. may be diluted with Glucose 5% or Sodium Chloride 0.9% Injection B.P. Water for Injections B.P. immediately before parenteral use. The remainder of solutions should be discarded after use: do not make up into multidose preparations.
MANUFACTURER	ONCOTEC PHARMA PRODUKTION GMBH AM PHARMAPARK 06861 DESSAU-ROSSLAU ALLEMAGNE	Hospira Australia Pty Ltd, 1-5, 7-23 and 25-39 Lexia Place, Mulgrave, VIC 3170, Australia

NOTABLE DIFFERENCES IN THE FRENCH AND IRISH CARTONS

PRODUCT NAME	**FLUOROURACILE PFIZER 50 mg/ml, solution à diluer pour perfusion** (FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion)	**Fluorouracil 25 mg/ml Solution for Injection or Infusion**
CONTENTS OF CARTON	Box of 6 vials of Fluorouracil 50 mg/ml Pack size 1 g/20 ml	Box of 1 vial Fluorouracil 25 mg/ml Pack size 2.5 g/100 ml
MARKETING AUTHORISATION HOLDER	**PFIZER HOLDING FRANCE** 23-25 AVENUE DU DOCTEUR LANNELONGUE 75014 PARIS	Pfizer Healthcare Ireland 9 Riverwalk National Digital Park Citywest Business Campus Dublin 24 Ireland
MARKETING AUTHORISATION NUMBER	34009 572 532 8 8	PA 0822/223/001

Pfizer Healthcare Ireland
9 Riverwalk, National Digital Park,
Citywest Business Campus, Dublin 24
Telephone: 01 4676500 Facsimile 01 4676501
Freephone: 1800 460 900
www.pfizer.ie

Further Information

FLUOROURACILE PFIZER 50 mg/ml, solution à diluer pour perfusion (FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion, pack size 1 g/20 ml) can be ordered through your normal wholesaler.

Please note expiry of the FLUOROURACILE PFIZER 50 mg/ml, solution à diluer pour perfusion (FLUOROURACILE PFIZER 50 mg/mL, concentrate for solution for infusion, pack size 1 g/20 ml) is 28.02.2023.

Please ensure all relevant staff and patients are made aware of the content of this letter and that the information is communicated to the patient.

If you have any questions, please contact:

Pfizer Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS or Tel: 1800 633363 and ask for Medical Information.

Call for adverse event reporting:
You can assist us with monitoring the safety of Fluorouracil 25 mg/ml Solution for Injection or Infusion. Accordingly, Healthcare professionals should report any suspected adverse events associated with the use of Fluorouracil 25 mg/ml Solution for Injection or Infusion to Pfizer Medical Information on 1800 633 363.

Alternatively, this information may be reported to the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Yours sincerely

_____
Róisín Flynn, MB BCh BAO
Medical Lead, Hospital Business Unit