Bundesinstitut
für Arzneimittel
und Medizinprodukte

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Antrag vom 15.07.2022 auf Erteilung einer Gestattung gemäß §§ 10 Absatz 1a und 11 Absatz 1c Arzneimittelgestz (AMG) – Einfuhr und Inverkehrbringen von Fluorouracil PhaRes 50 mg/ml Injektionslösung

Arzneimittelbezeichnung	Zulassungsinhaber	Zulassungsnummer
Fluorouracil PhaRes 50 mg/ml Injektionslösung	**Pharma Resources GmbH**	**89558.00.00**

Sehr geehrte Damen und Herren,
auf Ihren mit E-Mail vom 15. Juli 2022 gestellten Antrag ergeht folgender

BESCHEID:

1. Es wird im Einzelfall gestattet, dass das o. g. Arzneimittel mit der für den englischen Markt bestimmten und damit mit einer in einer anderen als der deutschen Sprache verfassten Kennzeichnung und Packungsbeilage in den Verkehr gebracht wird.
2. Diese Gestattung ist befristet bis zum 31. Dezember 2022.

Begründung:

Zu 1.

Nach §§ 10 Absatz 1a und 11 Absatz 1c AMG kann die zuständige Bundesoberbehörde im Fall eines drohenden oder bestehenden Versorgungsengpasses auf Antrag des Zulassungsinhabers im Einzelfall gestatten, dass ein Arzneimittel, das durch Ärzte unmittelbar an Patienten angewendet wird, befristet mit einer Kennzeichnung und Packungsbeilage in einer anderen als der deutschen Sprache in den Verkehr gebracht wird.

Diese Voraussetzungen sind vorliegend erfüllt.

Bei der von Ihnen mit dem Antrag vorgelegten und für den englischen Markt bestimmten Kennzeichnung/Packungsbeilage handelt es sich um eine Kennzeichnung/Packungsbeilage in einer anderen als der deutschen Sprache.

Die gesetzlichen Voraussetzungen sind vorliegend erfüllt, da das in Rede stehende Arzneimittel unmittelbar durch Ärzte an Patienten abgegeben wird.

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Fluorouracil PhaRes 50 mg/ml Injektionslösung ist für folgende Anwendungsgebiet zugelassen:

- Fortgeschrittenes oder metastasiertes kolorektales Karzinom
- Adjuvante Chemotherapie des Kolonkarzinoms Stadium III (T1-4 N1-2) nach vorausgegangener kurativer Resektion des Primärtumors
- Adjuvante Chemotherapie des Rektumkarzinoms Stadium II (T3-4) und III (T1-4 N1-2) nach vorausgegangener kurativer Resektion des Primärtumors
- Fortgeschrittenes Magenkarzinom
- Fortgeschrittenes Pankreaskarzinom
- Fortgeschrittenes Ösophaguskarzinom
- Fortgeschrittenes und/oder metastasiertes Mammakarzinom
- Adjuvante Therapie des primären invasiven Mammakarzinoms
- Plattenepithelkarzinome des Kopf-Hals-Bereiches:
    - bei unvorbehandelten Patienten mit inoperablen lokal fortgeschrittenen Tumoren
    - bei Lokalrezidiven und Fernmetastasierung.

Im Rahmen der durch das BfArM aktuell durchgeführten Sachverhaltsermittlung wurde eine drohende versorgungsrelevante Lieferengpasssituation festgestellt. Aufgrund von aktuellen Lieferengpassmeldungen und Rückrufen stehen wirkstoff- und darreichungsgleiche Arzneimittel aktuell nicht in den Bedarf deckendem Umfang zur Verfügung. Das Inverkehrbringen der in Rede stehenden Ware dient der Sicherstellung der Patientenversorgung.

Aus medizinischer Sicht ist 5-Fluorouracil ein unverzichtbarer Bestandteil verschiedener Therapieregime, wie z.B. FOLFOX, FOLFIRI, in den oben genannten Tumortherapien. In diesen festen, evidenzbasierten Behandlungsregimen kann es nicht durch andere intravenös-verfügbare Arzneistoffe ausgetauscht werden, da deren Sicherheit und Wirksamkeit hierin nicht belegt sind und/oder dafür keine Zulassung besteht (z.B. Cetuximab in Kombination mit FOLFOX). Auch eine Umstellung der Patienten auf andere Arzneimittel oder Regime innerhalb einer Behandlung ist nicht möglich, um die Patienten nicht zu gefährden und den Therapieerfolg nicht zu beeinträchtigen. Gegebenenfalls könnte jedoch alternativ die Anwendung von oralem Capecitabin in einzelnen Indikationsstellungen möglich sein.

Zu 2.
Die Befristung erfolgt antragsgemäß, stützt sich auf §§ 10 Absatz 1a und § 11 Absatz 1c AMG und ist im genannten Zeitraum ausreichend, um den drohenden Versorgungsengpass mit dem o. g. Arzneimittel auf dem deutschen Markt abzuwenden. Nach derzeitigem Informationsstand ist ab 1. Januar 2023 wieder von einer ausreichenden Verfügbarkeit von Ware in deutscher Aufmachung auszugehen.

Hinweis:
Es wird empfohlen, aus Gründen der Nachvollziehbarkeit und Transparenz ein offizielles Informationsschreiben inklusive eines Links zur elektronischen Verfügbarkeit der Produktinformationstexte in deutscher Aufmachung jeder Lieferung beizufügen.

Rechtsbehelfsbelehrung:
Gegen diesen Bescheid kann innerhalb eines Monats nach Bekanntgabe Widerspruch erhoben werden. Der Widerspruch ist bei dem Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Bonn einzulegen.

Bonn, den 20.07.2022

Mit freundlichen Grüßen
Im Auftrag

Dr. Michael Horn

Anlagen

- Gebrauchsinformation – in englischer Aufmachung
- Äußere Umhüllung der Stärken 250mg/5ml und 1000mg/20ml – in englischer Aufmachung
- Etikett der Stärken 250mg/5ml und 1000mg/20ml – in englischer Aufmachung

Placeholder
for QR codes

Package leaflet: Information for the patient
Fluorouracil PhaRes 50 mg/ml solution for injection
Active substance: Fluorouracil
For use in adults.

Package leaflet: Information for the patient
Fluorouracil PhaRes 50 mg/ml solution for injection
Active substance: Fluorouracil
For use in adults.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fluorouracil PhaRes is and what it is used for?

Fluorouracil PhaRes is an anti-cancer medicine that is used alone or in combination with other anti-cancer medicines. Fluorouracil PhaRes belongs to a group of medicines called antimetabolites (pyrimidine analogues).

Therapeutic indications
- Advanced and/or metastatic cancer of the colon (large bowel) and rectum
- Adjuvant chemotherapy for stage III (T1-4 N1-2) colon (large bowel) cancer following prior removal of the primary tumour
- Adjuvant chemotherapy for stage II (T3-4) and III (T1-4 N1-2) rectal cancer following prior removal of the primary tumour
- Advanced gastric cancer
- Advanced pancreatic cancer
- Advanced oesophagus cancer
- Advanced and/or metastatic breast cancer
- Adjuvant treatment for primary invasive breast cancer
- Certain tumours of the head and neck:
  - for patients with locally advanced, inoperable tumours who have not previously received treatment
  - for locally recurrent tumours and distant metastases

2. What you need to know before you use Fluorouracil PhaRes?

Do not use Fluorouracil PhaRes
- if you are allergic to fluorouracil or any of the other ingredients of this medicine (listed in section 6).
- if your blood cell count is reduced (bone marrow depression), e.g. after previously receiving chemotherapy and/or radiotherapy.
- if you suffer from bleeding, inflammation of the oral mucosa, ulcers in the mouth and gastrointestinal tract, severe diarrhoea, severe kidney dysfunction, plasma bilirubin levels > 85 µmol/l.
- if you have severe blood count abnormalities, severe liver dysfunction, acute infections or are in a poor nutritional state.
- if you are if you are being treated now or have been treated in the last 4 weeks with brivudine as part of herpes zoster (chickenpox or shingles) therapy. You must not use Fluorouracil PhaRes as part of cancer chemotherapy if you are undergoing treatment with brivudine for Herpes zoster, or have received such treatment in the past four weeks. Combined treatment with fluorouracil and brivudine, fluorouracil may considerably intensify the side effects of Fluorouracil PhaRes. This interaction can be fatal. Hence, you must not use these medicines in combination with fluorouracil chemotherapy. You may start chemotherapy with fluorouracil four weeks at the earliest after completing herpes zoster treatment with brivudine.
  If you are being treated, or have recently been treated, for a Herpes zoster infection, please, tell your doctor which medicines you have taken.
- if you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency).
- if you are breastfeeding.

Note:
- The administration of active vaccines should not coincide with fluorouracil therapy. Patients should avoid coming into contact with persons receiving polio vaccines.

Warnings and precautions
Talk to your doctor or pharmacist before using Fluorouracil PhaRes,
- if you know that you have a partial deficiency in the activity of the enzyme dihydropyrimidine dehydrogenase (DPD)
- if you have a family member who has partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)
- if you have problems with your heart. Tell your doctor if you experience any chest pain during treatment.

DPD deficiency: DPD deficiency is a genetic condition that is not usually associated with health problems unless you receive certain medicines. If you have DPD deficiency and take Fluorouracil PhaRes, you are at an increased risk of severe side effects (listed under section 4 Possible side effects). It is recommended to test you for DPD deficiency before start of treatment. If you have no activity of the enzyme you should not take Fluorouracil PhaRes. If you have a reduced enzyme activity (partial deficiency) your doctor might prescribe a reduced dose. If you have negative test results for DPD deficiency, severe and life-threatening side effects may still occur.

Contact your healthcare provider immediately, if you experience the following signs or symptoms: new onset of confusion, disorientation, or otherwise altered mental status, difficulty with balance or coordination, visual disturbances. These could be signs of encephalopathy which can lead to coma and death, if left untreated.

Fluorouracil PhaRes should only be administered by doctors experienced in tumour therapy.

The following checks are recommended before and during treatment with fluorouracil (the frequency of such procedures depends on the general condition, dose and concomitant medication):

Daily inspection of the oral cavity and the throat for mucosal changes; before each dose of fluorouracil:

blood count including differential blood count and platelets; kidney retention values; liver function values

Any existing infections should be treated prior to commencing therapy with Fluorouracil PhaRes.

If you are taking phenytoin for epileptic attacks. Simultaneous use of phenytoin and Fluorouracil PhaRes can cause an increased the concentration of phenytoin in the blood. Your blood should therefore be checked regularly for elevated phenytoin levels.

Precautions for use:
If any of the following signs of toxicity occur, the medication must be stopped immediately:

Rapid decrease in white blood cells (leukocytes) during treatment or development of a reduced white blood cell count (leukopenia; leukocyte count < 3,500/µl), reduced number of platelets (thrombocytopenia; platelet count < 100,000/µl), inflammation of the oral mucosa, inflammation of the oesophagus or throat, inflammation of the mucous membranes, diarrhoea, ulceration and bleeding of the gastrointestinal mucosa, bleeding of any location, uncontrollable vomiting, as well as any other severe side effects occur (e.g. nervous system disorders, heart damage). Once the changes in blood count have resolved (restoration of the leukocytes to at least 3,500/µl, platelets to at least 100,000/µl), treatment may be resumed – if necessary at a reduced dose – provided there are no other side effects (see above) that prevent continuation of therapy.

Damage to the intestinal wall requires symptomatic treatment appropriate to the severity of the damage, e.g. fluid replacement. Mild diarrhoea may respond to medicines used for treating diarrhoea. Such medicines will not suffice in moderate to severe diarrhoea.

Fluorouracil/folinic acid:
Folinic acid can increase the risk of toxicity from fluorouracil, especially in elderly or debilitated patients. The most common, potentially dose-limiting symptoms are a reduced number of white blood cells, inflammation of the mouth and throat, inflammation of the gastrointestinal tract and/or diarrhoea. If folinic acid and fluorouracil are combined, the dose of fluorouracil must be reduced to a greater degree in the event of toxicity than when fluorouracil is administered alone.

Treatment with a combination of fluorouracil and folinic acid should not be initiated or continued in patients with gastrointestinal side effects (gastrointestinal toxicity), regardless of the severity, until the patient exhibits no further symptoms.

Since diarrhoea can be a sign of gastrointestinal toxicity, patients with diarrhoea must be monitored closely until no further symptoms occur, as rapid deterioration in the clinical condition can occur, possibly resulting in death. If diarrhoea and/or inflammation of the oral mucosa occur, it is advisable to reduce the dose of fluorouracil until the symptoms have resolved completely. Especially the elderly and patients who are in poor general health due to their disease are at an increased risk of developing these toxicities. Particular caution is therefore required in these patients.

In elderly patients and patients who have previously undergone radiotherapy, it is recommended to start with a reduced dose of fluorouracil.

In patients receiving a combination of fluorouracil/folinic acid, the calcium level should be monitored and calcium supplementation should be provided if the calcium level is low.

The prothrombin value must be closely monitored in patients on anticoagulants who are also given fluorouracil (alone or combined with levamisole).

Other medicines and Fluorouracil PhaRes
Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines. This is extremely important, as taking more than one medicine at the same time can strengthen or weaken the effect of the medicines

Please note that this information also applies to medicines used recently.

You must not take brivudine (an anti-viral medicine for the treatment of shingles or chickenpox) at the same time as fluorouracil treatment (including during any rest periods when you are not taking any fluorouracil infusion).

If you have taken brivudine you must wait for at least 4 weeks after stopping brivudine before starting to take fluorouracil. See also section "Do not take Fluorouracil PhaRes".

Also, you need to be particularly careful if you are using medicines for treating epileptic attacks (phenytoin).

All treatment measures that can cause the condition of the patient to deteriorate or impair bone marrow function can intensify the adverse effects of fluorouracil. Fluorouracil can intensify the adverse skin reactions caused by radiotherapy.

Folinic acid enhances the effect of fluorouracil. The clinical consequence of such an interaction is increased gastrointestinal toxicity (adverse effects on the gastrointestinal tract) with serious, sometimes fatal cases of diarrhoea, but also an increased bone marrow toxicity with impairment of blood formation. An increased number of such deaths were reported in particular from the weekly administration of single intravenous bolus doses of fluorouracil at 600 mg/m² body surface area if combined with folinic acid.

Both cimetidine and interferons can increase the plasma concentration of fluorouracil. This may potentiate the adverse effects of fluorouracil.

Liver damaging effects are often observed during concomitant treatment of fluorouracil and levamisole. Such damage is mostly expressed as an increase in the corresponding blood values (alkaline phosphatase, transaminases or bilirubin).

During concomitant treatment with metronidazole, an increase of fluorouracil serum levels and increased toxicity was observed. The simultaneous administration of both medications should be avoided.

One study found a higher risk of thromboembolism in female patients with breast cancer (malignant tumour in the breast) under treatment with a combination of cyclophosphamide, methotrexate, fluorouracil and tamoxifen.

Thiazide diuretics may enhance the toxic effects of anti-cancer agents on the bone marrow if given at the same time.

The simultaneous administration of vinorelbine and fluorouracil/folinic acid can cause severe mucositis (inflammation of the mucous membranes), resulting in death.

In some cases, patients on anticoagulant therapy with warfarin were found to have a decreased prothrombin value, if they were given fluorouracil (alone or combined with levamisole) at the same time.

Certain laboratory tests (methods for detecting bilirubin and 5-hydroxyindoleacetic acid in the urine) may show increased or false-positive results during treatment with fluorouracil.

Gemcitabine can increase the systemic fluorouracil load.

Both the efficacy and toxicity of fluorouracil may be intensified by combining fluorouracil with other cytotoxic drugs (e.g. cyclophosphamide, vincristine, methotrexate, cisplatin, doxorubicin), interferon-alpha or folinic acid.

When combined with other medicines that suppress the bone marrow, a dose adjustment is necessary; prior or simultaneous radiotherapy can necessitate a dose reduction. The negative effect of anthracyclines on the heart may be increased.

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

The concurrent administration of allopurinol can reduce the toxicity and efficacy of fluorouracil.

The efficacy of fluorouracil may be reduced by the administration of chlordiazepoxide, disulfiram, griseofulvin and isoniazid.

Vaccines: Fluorouracil decreases the normal body defence, thereby impairing the immune response. Live vaccines can lead to increased viral replication.

The occurrence of the hemolytic-uremic syndrome has been reported for treatment with fluorouracil in combination with mitomycin.

Most important incompatibilities (chemical intolerance)
Fluorouracil must not be mixed for administration with other medicinal products.

5-Fluorouracil must not be mixed with folinic acid in the same i.v.-injection or infusion.

Fluorouracil may only be diluted with sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution.

Chemical intolerance (incompatibilities) has been reported with the following substances: cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, leucovorin, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutritional solutions, vinorelbine.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. If you are a woman of childbearing potential, you must not become pregnant during treatment and use an effective method of contraception while taking this drug and at least for 6 months afterwards.

If pregnancy occurs during your treatment you must inform your doctor and should genetic counselling.

Breast-feeding
Since it is not known whether fluorouracil passes into breast milk, breast-feeding must be discontinued before treatment with Fluorouracil PhaRes.

Fertility
If you are a man you should avoid to father a child during and for up to 3 months following end of treatment with Fluorouracil PhaRes. You are advised to seek conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Fluorouracil PhaRes.

Driving and using machines
Treatment with fluorouracil can cause nausea, vomiting and hypersensitivity reactions with decrease in blood pressure which can indirectly influence the ability to drive a motor vehicle or operate machinery. In such cases, do not drive a car or any other type of vehicle! Do not operate electrical tools or machines! Do not work without secure hold!

3. How to use Fluorouracil PhaRes?

Treatment with fluorouracil should only be administered by doctors experienced in the treatment of cancer, at a hospital or in cooperation with a hospital. Since the methods of administration and dosage of fluorouracil vary considerably and an optimal dosage has not yet been determined, only general recommendations can be made. Details should be obtained from the current literature.

Monotherapy
If fluorouracil is used as monotherapy, it is generally given at doses of 370-400 mg fluorouracil/m² body surface area (but sometimes at significantly higher doses) at varying time intervals and using different methods of administration.

Polychemotherapy
When combined with other cytostatic agents, fluorouracil is used at different dosages and with different methods of administration. The reported dosage range is generally between 500 to 600 mg/m² body surface area intravenous, administered at specific times during the respective combined chemotherapeutic regimen.
The exact dosage as part of polychemotherapy should be determined from treatment protocols that have proved effective for the relevant disease.

Adults
Fluorouracil is used either as monotherapy or as part of a polychemotherapeutic regimen.

Advanced or metastatic cancer of the colon (large bowel) and rectum
Various treatment protocols and doses are used without a particular optimal dosage regimen.

The following regimens have been used in adults and the elderly in the treatment advanced or metastatic colorectal carcinoma and are provided as examples. There are no data available on the use of these combinations in children.

Two-month treatment protocol
On two consecutive days (days 1 and 2 of the cycle) every two weeks, a two-hour intravenous infusion of 200 mg/m² body surface area folinic acid is followed by a bolus injection of fluorouracil at 400 mg/m² body surface area followed by infusion of 600 mg/m² body surface area fluorouracil over 22 hours.

Weekly treatment protocol
Once weekly, a two-hour intravenous infusion of 500 mg/m² body surface area folinic acid is followed by an intravenous bolus injection of fluorouracil at a dose of 500 mg/m² body surface area one hour after starting the folinic acid infusion. One cycle consists of six weekly treatments followed by an interval of two weeks.

Monthly treatment protocols
On five consecutive days, a bolus injection of folinic acid (20 mg/m² body surface area) is followed by an intravenous bolus injection of fluorouracil at a dose of 425 mg/m² body surface area; this is repeated every four to five weeks.

On five consecutive days, a bolus injection of folinic acid (200 mg/m² body surface area) is followed by an intravenous bolus injection of fluorouracil at a dose of 370 mg/m² body surface area; this is repeated every four weeks.

The number of repeat cycles is left to the discretion of the treating doctor and depends on the response to the therapy and/or the occurrence of unacceptable side effects. Six cycles of combination therapy are usually administered if using the weekly or monthly treatment protocol.

Adjustment of the dosage for combination therapy with folinic acid
In combination therapy with folinic acid, an adjustment of fluorouracil doses and treatment intervals may be necessary depending on the condition of the patient, the clinical response and dose-limiting toxicity. The folinic acid dosage does not need to be reduced.

Adjuvant chemotherapy for stage III (T1-4 N1-2) colon (large bowel) cancer following prior removal of the primary tumour
The following dosage regimens can be recommended at present:

Weekly treatment protocol
Once weekly for six weeks, a two-hour intravenous infusion of folinic acid (500 mg/m² body surface area) is followed by an intravenous bolus of fluorouracil at a dose of 500 mg/m² body surface area one hour after starting the folinic acid infusion. Six cycles, with a two-week interval between cycles, are recommended. Irrespective of dose adjustments or treatment interruptions, the duration of therapy should not exceed one year.

Treatment protocol with "low-dose" folinic acid
On five consecutive days, an intravenous bolus of 425 mg/m² body surface area fluorouracil is administered immediately after a bolus injection of folinic acid (20 mg/m² body surface area) for a total of six cycles The treatment cycles are repeated after 4 and 8 weeks, and thereafter every 5 weeks.

Dosage adjustments may be necessary depending on the occurrence of toxic side effects.

Suspension of therapy due to blood count changes

Leukocytes < 3,500 or thrombocytes < 100,000	Suspend therapy until increase of leukocytes (≥ 3,500) and thrombocytes (≥ 100,000)
Leukocytes < 2,500 or thrombocytes < 75,000	Suspend therapy until increase of leukocytes (≥ 3,500) and thrombocytes (≥ 100,000) but for at least 3 weeks

Suspension of therapy due to gastrointestinal changes

Light to moderate stomatitis and/or slight diarrhoea (2 stools/day)	Suspend therapy until nomalisation
Severe stomatitis and/or diarrhoea (3-6 stools/day)	Suspend therapy until normalisation - but for at least 3 weeks
Gastrointestinal bleeding, disabling diarrhoea (≥ 7 stools/day) ± exfoliative dermatitis	Stop therapy!

Adjuvant chemotherapy for stage II (T3-4) and III (T1-4 N1-2) rectal cancer following prior removal of the primary tumour
As part of radiochemotherapy, fluorouracil is given prior to radiotherapy as an intravenous bolus of 500 mg/m² body surface area on days 1 to 5 of the first and 5th treatment weeks. During subsequent radiotherapy, fluorouracil is given at the same dose on days 1 to 3 of the 9th and 13th treatment week and thereafter (week 4 and 8 after completing radiotherapy) as an intravenous bolus of 450 mg/m² body surface area on days 1 to 5.

Advanced pancreatic cancer
As monochemotherapy, in single daily doses of 400-500 mg/m² body surface area as intravenous bolus injection or of 1000 mg/m² body surface area as a continuous intravenous infusion.

Advanced gastric cancer
As monochemotherapy or as part of polychemotherapy in single daily doses of 500-600 mg/m² body surface area as intravenous bolus injections.

Advanced cancer of the oesophagus
In combination with cisplatin, fluorouracil is given as a 24-h continuous infusion at a dose of 1000 mg/m² body surface area on days 1 to 5 of a treatment cycle; this is repeated every 3 (-4) weeks.

Concerning the use of fluorouracil/cisplatin as part of a combined radio-chemotherapy, please refer to the literature.

Advanced or metastatic breast cancer
As part of polychemotherapy, fluorouracil is used as single daily intravenous doses of 500-600 mg/m² body surface area (e.g. CMF, FAC).

Adjuvant treatment for primary invasive breast cancer
Fluorouracil PhaRes is administered as single daily IV doses of 500-600 mg/m² body surface area as part of polychemotherapy (e.g. CMF, FEC, FAC).

Cancer of the head and neck area
- For patients with locally advanced, inoperable tumours who have not been treated previously:
  As part of combined radiochemotherapy (radiotherapy plus cisplatin/fluorouracil), fluorouracil is given as a continuous infusion for 24 hours at a dose of 1000 mg/m² body surface area on days 1 to 5 of a treatment cycle (repeated every 3 to 4 weeks).
- For locally recurrent tumours and distant metastases:
  Depending on the general health and any existing comorbidities, fluorouracil is given as a continuous infusion for 24 hours at a dose of 1000 mg/m² body surface area on days 1 to 5 of a treatment cycle in combination with cisplatin (repeated every 3 weeks) and on days 1 to 4 of a treatment cycle in combination with carboplatin (repeated every 3 weeks).

Discontinuation of therapy, dose reduction
If any of the following toxic symptoms occur, treatment with fluorouracil must be stopped immediately:
- Reduced number of white blood cell (leukopenia) (< 2,500/µl)
- Reduced number of platelets (thrombocytopenia) (< 75,000/µl)
- Inflammation in the mouth and/or oesophagus
- Vomiting that cannot be controlled by an antiemetic agent
- Diarrhoea
- Ulcers and bleeding in the gastrointestinal tract
- Increased bleeding tendency
- Nervous system disorders
- Heart disorders

Once the white blood cells (leukocytes) (>3,500/µl) respectively platelets (thrombocytes) (>100,000/µl) have increased again, treatment can be resumed - if necessary at a reduced dose - provided there are no overall adverse effects (see above) that prevent continuation of therapy.

Use in children
There is insufficient experience in safety and efficacy of Fluorouracil PhaRes in children. Fluorouracil PhaRes should not be used in children under 18 years of age.

Patients with impaired liver or kidney function
Impaired liver or kidney function does not require a dose reduction. Only if the liver and kidney function are both impaired, a dose reduction should be considered - in more serious cases by a third to a half.

How and when should Fluorouracil PhaRes be used?
Fluorouracil PhaRes is administered intravenously as a bolus or (continuous) infusion.

Duration of administration
The treating doctor should decide on the duration of treatment, depending on the treatment protocol. Treatment should be discontinued if the tumour does not respond, if the disease progresses, or if side effects occur that prevent treatment from being continued.

How long should Fluorouracil PhaRes be used?
The treating doctor will determine the duration of treatment taking into account clinical symptoms, the applied treatment protocol (treatment plan) and individual therapeutic setting. If the tumour does not respond, the disease progresses and/or intolerable side effects develop, Fluorouracil PhaRes use should be discontinued.

Fluorouracil PhaRes is administered in treatment cycles. Depending on the treatment schedule, a treatment-free interval should be left between the last day of one treatment cycle and the first day of the next cycle until the blood count has recovered (see "Do not use Fluorouracil PhaRes").

If you use more Fluorouracil PhaRes than you should
Symptoms of overdose include severe gastrointestinal complaints with diarrhoea, serious damage to the bone marrow (myelosuppression), which generally develops 10-14 days after starting treatment (but may occur suddenly), as well as severe inflammation of the mucous membranes. Treatment for severe toxicity should take place in a hospital setting. If the damage to the bone marrow is severe, it involves replacement of the deficient blood components and antibiotic therapy under certain circumstances. It may be necessary to transfer the patient to a sterile room. Administration of Fluorouracil PhaRes should be stopped immediately if signs of intoxication develop.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any of the following happen, tell your doctor immediately:
- chest pains
- shortness of breath

Other undesirable effects may be:

Very common (may affect more than 1 in 10 people):
- decreased hematopoietic function of the bone marrow, reduction in certain blood cells (leukopenia, neutropenia and thrombocytopenia)
- somnolence, general weakness, fatigue and listlessness
- ECG changes typical for ischaemia or cardiomyopathy, angina pectoris
- nausea, vomiting, loss of appetite (anorexia), inflammation of the oral mucosa (stomatitis), oesophagus, throat, rectum, oesophagitis (with retrosternal burning), pharyngitis (with dysphagia), proctitis (with watery diarrhoea)
- mild to total hair loss, skin inflammation (dermatitis), 'hand-foot syndrome with sensory disturbances along with redness, swelling, pain and flaking of the skin on the palms of the hands and soles of the feet. Hand-foot syndrome occurs more often after continuous intravenous infusion than after intravenous bolus injection of fluorouracil.
- vomiting and nausea
- (severe) change in the mucous membranes
- more severe diarrhoea and reduction of bodily fluids, which can necessitate hospitalization for treatment and even result in death
- infections

Common (may affect up to 1 in 10 people):
- decreased numbers of certain blood cells (agranulocytosis), severe decrease in the numbers of blood cells of all systems (pancytopenia), anaemia
- increased uric acid concentration in the blood (hyperuricaemia)
- non-inflammatory disorders or damage to the brain (encephalopathies) with corresponding symptoms (cerebellar ataxia, muscle weakness, disorientation, confusion and coma) occur especially after infusion of high doses of fluorouracil
- bronchial spasm (bronchospasm)
- dry, cracked (fissured) skin
- low white blood cells accompanied by fever

Uncommon (may affect up to 1 in 100 people):
- allergic reactions as severe as anaphylactic shock, fever
- eye twitching (nystagmus), dizziness, Parkinson's symptoms, pyramidal tract signs, headache and euphoria.
- inflammation of the optic nerve (optic neuritis), double vision (diplopia), decreased visual acuity, photophobia, conjunctivitis (sometimes with ulcerations), inflammation of the eyelids (blepharitis), blurred vision, fibrosis of the lacrimal ducts, impaired ocular motility, excessive lacrimation.
- heart attack (myocardial infarction, in some cases fatal), arrhythmias, heart muscle weakness (congestive heart failure/ myocardial insufficiency), inflammatory disease of the heart muscle (myocarditis, in some cases fatal), chest pain, left-ventricular dysfunction, cardiogenic shock
- inflammation of the veins (thrombophlebitis)
- severe damage to the intestinal wall with bloody diarrhoea, loss of fluids and blood poisoning (dehydration and sepsis, sometimes starting suddenly and life-threatening), liver cell damage
- death of the cells in the nasal bone
- renal failure
- impaired production of sperm and impaired ovulation

Rare (may affect up to 1 in 1,000 people):
- hives (urticaria), light sensitivity, increased pigmentation or depigmentation of the skin as well as diffuse nail changes (including pigment changes, nail detachment, nutritional deficiencies of the nails, pain and thickening of the nail bed, as well as inflammation of the nail groove)

Very rare (may affect up to 1 in 10,000 people):
- elevated total serum thyroxine (T4) and total serum triiodothyronine (T3) with no increase in free T4 and TSH and no clinical symptoms of an overactive thyroid (hyperthyroidism)
- cerebral infarction has been reported from combined chemotherapy (for example fluorouracil combined with mitomycin C or cisplatin); demyeliting disease (leukoencephalopathy), reversible after immediately stopping treatment, has been reported; patients with dihydropyrimidine dehydrogenase deficiency are possibly at greater risk. DWI (diffusion-weighed imaging) may be helpful in the diagnosis of leukoencephalopathy
- nosebleeds (epistaxis), low blood pressure (hypotension)
- individual cases of liver necrosis (in some cases fatal)
- skin rash (mostly involving itchy, nodular pustules on the entire body)
- isolated reports of prolonged coagulation time if Fluorouracil PhaRes has been administered in conjunction with warfarin. Gemcitabine might increase the systemic availability of fluorouracil
- cardiac arrest

Not known (frequency cannot be estimated from the available data):
- inflammation of the gallbladder (cholecystitis)
- hyperammonaemic encephalopathy (brain dysfunction caused by elevated ammonia)
- pericarditis
- inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints and fever (cutaneous lupus erythematosus [CLE])
- heart disease that presents with chest pain, shortness of breath, dizziness, fainting, irregular heartbeat (stress cardiomyopathy)
- air in the intestinal wall
- serious condition that presents with difficulty breathing, vomiting and abdominal pain with muscle cramps (lactic acidosis)
- condition characterised by headache, confusion, seizures and changes in vision (posterior reversible encephalopathy syndrome [PRES])
- serious complication with rapid break down of cancer cells causing high levels of uric acid, potassium and phosphate (tumour lysis syndrome)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fluorouracil PhaRes?

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and container. The expiry date refers to the last day of that month.

Storage conditions:
Keep vial in the outer carton in order to protect from light.
Store between 15 °C and 25 °C.
Do not refrigerate or freeze. If stored at low temperatures, formation of precipitates is possible.

Shelf-life after opening
Discard any unused content once opened!

Shelf life after preparing the ready-to-use solution
From a microbiological point of view the reconstituted mixture should be used immediately. If it is not used immediately, the user is responsible for storage times and storage conditions.
Provided the ready-to-use mixture has been prepared under controlled and validated aseptic conditions, this mixture should not be stored longer than 24 hours at room temperature (not above 25 °C) under exclusion of daylight.
The vials are intended for single use only. Discard any unused contents.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fluorouracil PhaRes contains
- The active substance is: Fluorouracil 1 ml of solution for injection contains 50 mg Fluorouracil.
- The other ingredients are: sodium hydroxide and water for injection.

What Fluorouracil PhaRes looks like and contents of the pack
Fluorouracil PhaRes is a clear, colourless to slightly yellow solution for injection.

Pack sizes:
Fluorouracil PhaRes is supplied in packs of 1 and 10 vials.
1 vial containing 5 ml solution for injection with 250 mg fluorouracil.
1 vial containing 10 ml solution for injection with 500 mg fluorouracil.
1 vial containing 20 ml solution for injection with 1000 mg fluorouracil.
1 vial containing 100 ml solution for injection with 5000 mg fluorouracil.

Marketing Authorisation Holder and Manufacturer:
MA Holder Germany: Pharma Resources GmbH

Manufactured by: Thymoorgan Pharmazie GmbH, Germany

This leaflet was last revised in March 2022.

The following information is intended for healthcare professionals only:

As with all cytotoxic agents, appropriate precautions should be taken when handling Fluorouracil PhaRes. Attention should be paid to the leaflet of the Professional Association for Health Services and Welfare, "Safe Handling of Cytostatics".

When handling fluorouracil, all contact with the skin and mucous membranes must be avoided. Due to the possible mutagenic and carcinogenic potential, increased safety measures are applicable to nursing staff and physicians. Preparation must take place under absolutely aseptic conditions; further safety measures include gloves, face masks, goggles and protective clothing. It is also advisable to work on a workbench with vertical laminar airflow (LAF). Disposal must take place in accordance with the hospital's regulations for disposal of cytostatics.

Pregnant staff must not handle fluorouracil.

Note
Use clear, colourless to slightly yellow solutions, only!

Precipitates may form in the solution if stored below 15 °C. Solutions should not be used if they have turned cloudy or a precipitate has formed. Only use freshly prepared solutions.

Shelf-life after opening
Fluorouracil PhaRes does not contain preservatives. If only part of the content of a vial is used, the remaining content must be discarded.

Shelf life after preparing the ready-to-use solution
Chemical and physical stability after reconstitution with sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution has been demonstrated for 24 hours if stored at 25 °C (room temperature).

From a microbiological point of view, the reconstituted solution should be used immediately unless the method of dilution rules out microbial contamination. If the solution for infusion is not used immediately, storage times and conditions prior to use are the responsibility of the user.

Incompatibilities
Fluorouracil PhaRes must not be mixed with other medicinal products unless their compatibility has been satisfactorily proven.

The solution for injection may only be diluted with sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) solution.

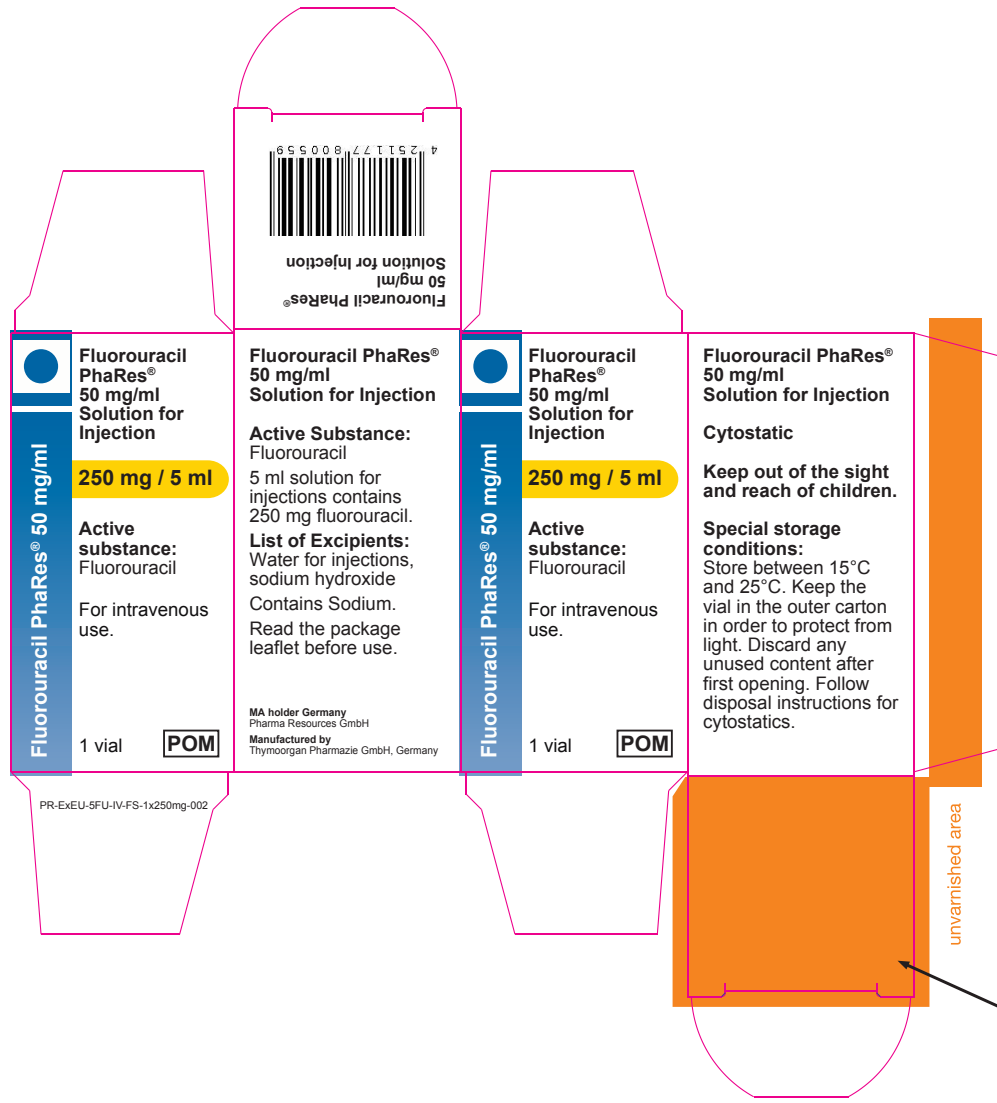
5-Fluorouracil must not be mixed with folinic acid in the same i.v.-injection or infusion.

Incompatibilities with the following substances have been reported: cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, leucovorin, methotrexate, metoclopramide, morphine, ondansetron, vinorelbine, solutions for parenteral nutrition.

Disposal
Any unused medicinal product or waste material, such as syringes and cannulae used for reconstitution and/or dilution of Fluorouracil PhaRes, must be disposed of in accordance with local requirements.

Job Title: Fluorouracil PhaRes Leaflet
Release Code: PR-ExEU-5FU-IV-GI-006
Size: 420 x 210 mm
Fonts: Arial
Created by: JG
Proofed:
Date: 21.04.2022

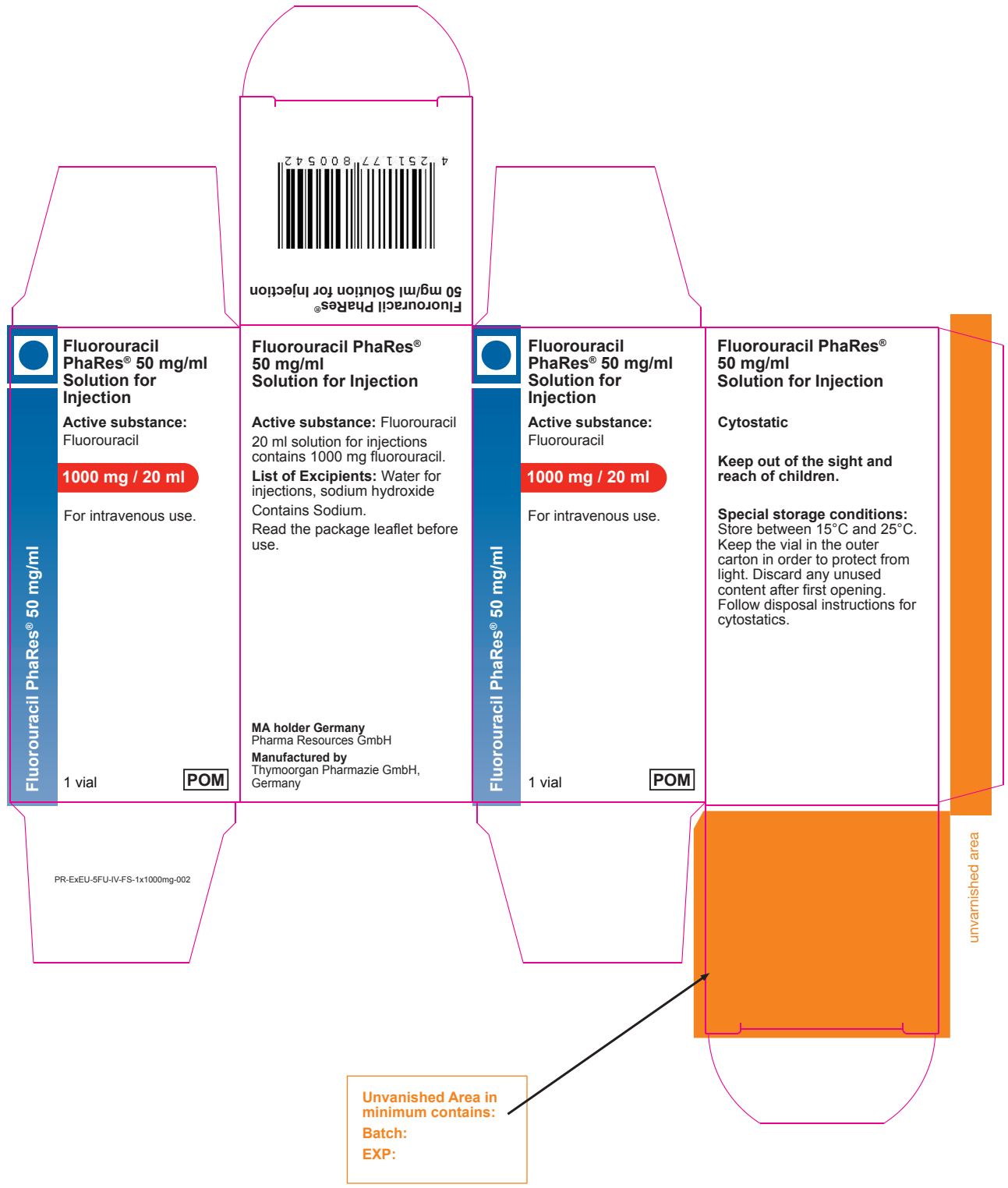
Note: Cutter guide is represented by magenta keyline. The cutter profile is not to be printed.



Job Title: Fluorouracil PhaRes 250 mg/5 ml Carton
Release Code: PR-ExEU-5FU-IV-FS-1x250mg-002
Size: 30x30x58 mm
Fonts: Arial
Created by: PS **Approved:**
Date: 09.05.2019
Colors:

- C: 100 M: 46 Y: 0 K: 18 (Pantone 301)
- C: 50 M: 24 Y: 0 K: 10 (Pantone 7454)
- C: 0 M: 16 Y: 100 K: 0 (Pantone 116)

Note: Cutter guide is represented by magenta keyline. The cutter profile is not to be printed.



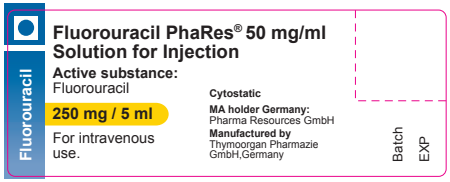
Job Title: Fluorouracil PhaRes 1000 mg/20 ml Carton
Release Code: PR-ExEU-5FU-IV-FS-1x1000mg-002
Size: 39.5 x 39.5 x 80.5 mm
Fonts: Arial
Created by: PS **Approved:**
Date: 09.05.2019
Colors:

C: 100 M: 46 Y: 0 K: 18 (Pantone 301)

C: 50 M: 24 Y: 0 K: 10 (Pantone 7454)

C: 0 M: 95 Y: 100 K: 0 (Pantone 485)

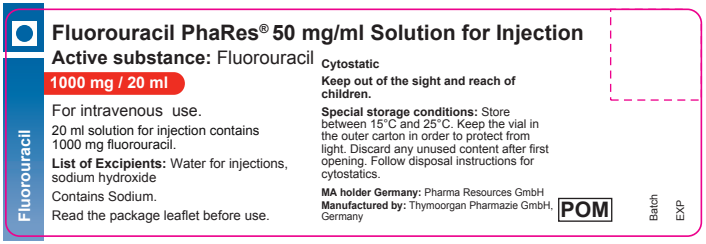
Note: Cutter guide is represented by magenta keyline. The cutter profile is not to be printed.



Job Title: Fluorouracil PhaRes 250 mg/5 ml Label
Release Code: PR-ExEU-5FU-IV-ET-250mg-002
Size: 58 x 22 mm
Fonts: Arial
Created by: PS
Approved:
Date: 09.05.2019
Colors:

- C: 100 M: 46 Y: 0 K: 18 (Pantone 301)
- C: 50 M: 24 Y: 0 K: 10 (Pantone 7454)
- C: 0 M: 16 Y: 100 K: 0 (Pantone 116)

Note: Cutter guide is represented by magenta keyline. The cutter profile is not to be printed.



Job Title: Fluorouracil PhaRes 1000 mg/20 ml Label
Release Code: PR-ExEU-5FU-IV-ET-1000mg-002
Size: 92 x 30 mm
Fonts: Arial
Created by: PS
Approved:
Date: 09.05.2019
Colors:

C: 100 M: 46 Y: 0 K: 18 (Pantone 301)

C: 50 M: 24 Y: 0 K: 10 (Pantone 7454)

C: 0 M: 95 Y: 100 K: 0 (Pantone 485)

Note: Cutter guide is represented by magenta keyline. The cutter profile is not to be printed.