Safeguarding public health

MHRA

Public Assessment Report

Fluorouracil 50mg/ml Solution for Injection or Infusion

PL 20851/0010
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Medicines and Healthcare products Regulatory Agency

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Fluorouracil 50mg/ml Solution for Injection or Infusion (PLs 20851/0010-3). These are prescription only medicines [POMs] used to treat various types of cancer, including breast cancer and lung cancer.

The active ingredient fluorouracil interferes with the production of DNA in cells.

The clinical data presented to the MHRA, before licensing, demonstrated that Fluorouracil 50mg/ml Solution for Injection or Infusion is essentially similar or equivalent to the approved product, Fluorouracil 50mg/ml Injection, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Fluorouracil 50mg/ml Solution for Injection or Infusion outweigh the risks, hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal product Fluorouracil 50mg/ml Solution for Injection or Infusion (PLs 20851/0010-3) to Wockhardt UK Limited on 19 September 2006. The product is a prescription only medicine.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Fluorouracil 50mg/ml Injection (PL 04515/0088), which was authorised in January 1996.

Fluorouracil 50mg/ml Solution for Injection or Infusion may be used alone, or in combination, for its palliative action in the management of common malignancies, particularly cancer of the colon and breast, either as a single agent or in combination with other cytotoxic agents.

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

PHARMACEUTICAL ASSESSMENT

PL NUMBER: **PLs 20851/0010-0013**
PRODUCT: **Fluorouracil 50mg/ml Solution for Injection or Infusion**
ACTIVE: **Fluorouracil**
COMPANY: **Wockhardt UK Limited**
E.C. ARTICLE: **10.1(a)(iii) of Directive 2001/83/EC**
LEGAL STATUS: **POM**

INTRODUCTION

These are generic applications for Marketing Authorisations in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83/EC, as amended, first paragraph (so-called generic application). The UK reference product is Fluorouracil 50mg/ml Injection, PL 04515/0088 licensed to Mayne Pharma plc on 4 January 1996.

DRUG SUBSTANCE

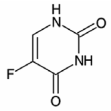
General information

Nomenclature

Chemical name: 5-fluoropyrimidine-2,4(1H,3H)-dione

INN: Fluorouracil

Structure



Molecular formula: $C_4H_3FN_2O_2$

Relative molecular mass: 130.1

General properties

Description: White to almost white crystalline powder

Manufacture

Manufacturer

Suitable manufacturing sites of the active substance have been named.

Manufacturing process

The manufacturing process is referenced to the Certificates of Suitability.

Characterisation

Referenced to the Certificates of Suitability.

Control of active substance

Specification

The finished product manufacturer specification provided covers the requirements of the European Pharmacopoeia. Additional limits are also included in the respective Certificates of Suitability.

Analytical test methods

Relevant details have been provided on the pharmacopoeial and non-pharmacopoeial test methods used.

Analytical test method validation

No validation data has been provided for the pharmacopoeial methods. Other methods are suitably validated.

Batch analyses

Reference has been made to the Certificate of Suitability. In addition Certificates of Analysis has been provided on a batch from each supplier as tested by the finished product manufacturer. All parameters are within specification and show a reasonable degree of comparability.

Reference standards

Details of appropriate reference standards have been provided.

Container closure system

Referenced to the Certificates of Suitability.

Stability

Stability data have been provided from batches manufactured at each of the active substance manufacturing sites. The batches show acceptable stability and support the proposed re-test period and shelf-life.

DRUG PRODUCT

Description and composition of the drug product

The composition of the product is summarised in the table below. The product is a sterile solution filled into colourless glass (type I) vials with a nominal volume of 6ml (250mg/5ml), 10ml (500mg/10ml), 20ml (1000mg/20ml), 50ml (2500mg/50ml) and 100ml (5000mg/100ml). The vials are closed with grey halobutyl rubber stoppers.

Ingredient	Function	Reference
Fluorouracil	Active	Ph.Eur.
Sodium hydroxide	pH adjustment	Ph.Eur.
Water for injections	Solvent	Ph.Eur.
Nitrogen	Inert gas	Ph.Eur.

Pharmaceutical development

Physicochemical and biological properties

It has been stated that the physicochemical and biological parameters are controlled with the specification. Sterility has been identified as an important biological property with data presented on seven batches covering the different presentations demonstrating compliance to sterility.

Manufacturing development

Data has been provided to justify the method of manufacture.

Manufacture

Batch formula

The batch formula is provided for suitable batch sizes.

Manufacturing process

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A written summary of the process has been included.

Control of critical steps

The critical steps are controlled by the proposed in-process controls.

Process validation or evaluation

Satisfactory data provided.

Control of excipients

Specification

Sodium hydroxide, water for injections and nitrogen have monographs in the European Pharmacopoeia. Batch analysis shows compliance with the respective monographs.

No excipients of human or animal origin have been used in the manufacture of the finished product.

Control of drug product

Specification

An acceptable finished product specification has been provided.

Analytical procedures

Details have been provided for the pharmacopoeial and non-pharmacopoeial methods.

Validation

Relevant validation data has been provided and is satisfactory.

Batch analyses

Batch analyses have been provided for six batches. All parameters are within specification and comparable.

Reference standards

Details of appropriate reference standards have been provided.

Container closure system

The injection vials are colourless glass, hydrolytic type I complying with the European Pharmacopoeia and the manufacturer's specification. The vials used have a 6ml, 10ml, 20ml, 50ml and 100ml capacity.

The closures are grey halobutyl rubber. The quality is in compliance with the European Pharmacopoeia and the manufacturer's specification.

The metallic cap is aluminium sheet. This item is not in contact with the finished product.

Relevant specifications have been provided which are considered acceptable. Relevant details of the methods have been provided. Drawings have also been supplied.

Stability

All dosage strengths have the same composition and only differ on fill volume. Consequently, data from one strength can be used as supporting data for the others.

Stability data has been presented on batches of the product packed in the proposed packaging. All vials have been stored upside down at 25ºC/60%RH and at 40ºC/75%RH. The data support a two year shelf-life with storage below 25ºC.

Stability in the infusion fluids has been determined in glucose 5% and sodium chloride 0.9% in glass bottles and polyethylene bags at concentrations of 0.35mg/ml and 15.0mg/ml. All parameters remained constant and within specification under all conditions in all packaging for up to 28 days at 25ºC.

ESSENTIAL SIMILARITY

Comparable impurity profiles have been provided for the finished product in comparison to the UK reference product.

SUMMARY OF PRODUCT CHARACTERISTICS
LABELLING
PACKAGE LEAFLETS

Satisfactory.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

Marketing authorisations can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required.

CLINICAL ASSESSMENT

PL NUMBER:	**PLs 20851/0010-0013**
PRODUCT:	**Fluorouracil 50mg/ml Solution for Injection or Infusion**
ACTIVE:	**Fluorouracil**
COMPANY:	**Wockhardt UK Limited**
E.C. ARTICLE:	**10.1(a)(iii) of Directive 2001/83/EC**
LEGAL STATUS:	**POM**

INTRODUCTION

These are generic applications for UK marketing authorisations.

Fluorouracil injection has been available on the UK market for decades. The product was first licensed in September 1972 to Roche Products Ltd. This licence has since been cancelled although there are a number of generic products currently available.

The applicant has submitted these applications under Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to one of the generic products as the reference medicinal product. The reference medicinal product in the UK is:

Product Name:	Fluorouracil 50mg/ml Injection
MAH:	Mayne Pharma plc
MA Number:	PL 04515/0088
Date approved:	4 January 1996

Fluorouracil is a fluorinated derivative of the pyrimidine base, uracil, and belongs to the antimetabolite group of cytostatic agents. This current application is indicated for use either alone or in combination, for its palliative action in the management of common malignancies particularly cancer of the colon and breast, either as single agent or in combination with other cytotoxic agents.

ASSESSMENT

The Summaries of Product Characteristics are satisfactory and compare well with the Summary of Product Characteristics of the generic reference product in the UK.

BIOEQUIVALENCE

Since these products are for parenteral (intravenous or intra-arterial) administration, there are no issues relevant to bioequivalence.

PATIENT INFORMATION LEAFLETS

These are satisfactory and in compliance with Directive 2001/83/EEC, as amended.

RECOMMENDATION

The recommendation is to grant marketing authorisations for these preparations.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Fluorouracil 50mg/ml Solution for Injection or Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the reference product Fluorouracil 50mg/ml Injection (PL 04515/0088). This is acceptable as the formulations are similar and the same routes of administration are proposed.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Fluorouracil 50mg/ml Injection.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Fluorouracil 50mg/ml Solution for Injection or Infusion on 19 August 2005.
2	The MHRA's assessment of the submitted quality data was completed on 25 February 2006.
3	Further information (quality) was requested from the company on 27 February 2006.
4	The MHRA's assessment of the submitted clinical data was completed on 2 March 2006.
5	Further information (clinical) was requested from the company on 2 March 2006.
6	The applicant's response to further information request (clinical) was received on 6 March 2006.
7	The applicant's response to further information request (quality) was sent in a letter dated 7 July 2006.
8	The MHRA completed its assessment of the applications on 19 September 2006.
9	The applications were determined on 19 September 2006.

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 50 mg of fluorouracil.

Each vial contains 250mg of fluorouracil in 5ml of solution

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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, either as a single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend 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 one gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight should be used as the basis for the calculation. Reduction of the dose is advisable in patients with any of the following:

1) Cachexia

2) Major surgery within preceding 30 days

3) Reduced bone marrow function

4) Impaired hepatic or renal function

Fluorouracil injection can be given by intravenous injection or, intravenous or intra-arterial infusion.

Adult Dose:

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: 15mg/kg bodyweight but not more than 1g per infusion, diluted in 300 - 500ml of 5% glucose or 9% sodium chloride injection and given by intravenous infusion at a rate of 40 drops per minute over four 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 - 15g has been reached.

Intravenous Injection: l2mg/kg bodyweight may be given daily for three days and then, if there is no evidence of toxicity, 6mg/kg on alternate days for three further doses. An alternative regimen is 15mg/kg as a single intravenous injection once a week throughout the course.

Intra-arterial Infusion: 5/7.5mg/kg 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 four to six weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5-15mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1g daily. A more recent alternative method is to give 15mg/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 fluorouracil 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 fluorouracil should be used.

Children:

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

Elderly:

Fluorouracil should be used in the elderly with similar considerations as with normal adult dosages.

4.3 Contraindications

Fluorouracil is contraindicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Fluorouracil should not be used in the management of non-malignant disease.

4.4 Special warnings and precautions for use

It is recommended that fluorouracil be given only by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites.

All patients should be admitted to hospital for initial treatment.

Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C) count commonly being observed between the seventh and fourteenth day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the thirtieth 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 $2000mm^3$, 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.

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the G.I. tract or haemorrhage at any site. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken therefore, in the selection of patients and adjustment of dosage.

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of fluorouracil. Care should be therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

There have been reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD).

4.5 Interaction with other medicinal products and other forms of interaction

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil - common drugs include methotrexate, metronidazole, leucovorin as well as allopurinol and cimetidine which can affect the availability of the active drug.

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

A clinically significant interaction has been reported between the antiviral sorivudine and fluorouracil , resulting from inhibition of dihydropyrimidine dehydrogenase by sorivudine or chemically related analogues. Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.

4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting.

Alopecia may be seen in a substantial number of cases, particularly females, but is reversible. Other side effects include dermatitis, pigmentation, changes in nails, ataxia and fever.

There have been reports of chest pain, tachycardia, breathlessness and E.C.G. changes after administration of Fluorouracil. Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.

Leucopenia is common and the precautions described above should be followed.

Systemic fluorouracil treatment has been associated with various types of ocular toxicity.

A transient reversible cerebellar syndrome has been reported following fluorouracil treatment. Rarely, a reversible confusional state may occur. Cases of leucoencephalopathy have also been reported.

Additionally, several other reports have been noted including:

Incidences of excessive lacrimation, dacryostenosis, visual changes and photophobia.

Palmar-Plantar Erythrodysesthesia Syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.

Thrombophlebitis / Vein Tracking.

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under "Other Undesirable Effects" and "Special Warnings and Precautions".

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01B C02, Pyrimidine Analogue

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

5.2 Pharmacokinetic properties

After intravenous administration, fluorouracil is distributed through the body water and disappears from the blood within three hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil ready enters the C.S.F and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependent. Following a single intravenous dose of fluorouracil approximately 15% of the dose is excreted unchanged in the urine within six hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Preclinical information has not been included because the toxicity profile of fluorouracil has been established after many years of clinical use. Please refer to section four.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Fluorouracil is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, other anthracyclines and possibly methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

6.3 Shelf life

24 months

After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4 Special precautions for storage

Unopened: Do not store above 25°C
After dilution: Do not store above 25°C (see 6.3 Shelf Life).

Chemical and physical in use stability of fluorouracil solutions with a concentration of 0.35mg/ml and 15.0mg/ml prepared in glucose 5% or sodium chloride 0.9% has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Packs* of one, five or ten Type I colourless glass 6ml vials stoppered with a halobutyl stopper sealed with an aluminium cap.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Cytotoxic Handling Guidelines

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Fluorouracil injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with a absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

Preparation Guidelines

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal

Syringes, vials and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Diluents

Fluorouracil injection may be diluted with glucose 5% injection or sodium chloride 0.9% injection or water for injections immediately before parenteral use.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20851/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2006

10 DATE OF REVISION OF THE TEXT

19/09/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 50 mg of fluorouracil.

Each vial contains 500mg of fluorouracil in 10ml of solution

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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, either as a single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend 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 one gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight should be used as the basis for the calculation. Reduction of the dose is advisable in patients with any of the following:

1) Cachexia

2) Major surgery within preceding 30 days

3) Reduced bone marrow function

4) Impaired hepatic or renal function

Fluorouracil injection can be given by intravenous injection or, intravenous or intra-arterial infusion.

Adult Dose:

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: 15mg/kg bodyweight but not more than 1g per infusion, diluted in 300 - 500ml of 5% glucose or 9% sodium chloride injection and given by intravenous infusion at a rate of 40 drops per minute over four 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 - 15g has been reached.

Intravenous Injection: l2mg/kg bodyweight may be given daily for three days and then, if there is no evidence of toxicity, 6mg/kg on alternate days for three further doses. An alternative regimen is 15mg/kg as a single intravenous injection once a week throughout the course.

Intra-arterial Infusion: 5/7.5mg/kg 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 four to six weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5-15mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1g daily. A more recent alternative method is to give 15mg/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 fluorouracil 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 fluorouracil should be used.

Children:

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

Elderly:

Fluorouracil should be used in the elderly with similar considerations as with normal adult dosages.

4.3 Contraindications

Fluorouracil is contraindicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Fluorouracil should not be used in the management of non-malignant disease.

4.4 Special warnings and precautions for use

It is recommended that fluorouracil be given only by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites.

All patients should be admitted to hospital for initial treatment.

Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C) count commonly being observed between the seventh and fourteenth day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the thirtieth 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 $2000mm^3$, 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.

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the G.I. tract or haemorrhage at any site. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken therefore, in the selection of patients and adjustment of dosage.

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of fluorouracil. Care should be therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

There have been reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD).

4.5 Interaction with other medicinal products and other forms of interaction

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil - common drugs include methotrexate, metronidazole,

leucovorin as well as allopurinol and cimetidine which can affect the availability of the active drug.

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

A clinically significant interaction has been reported between the antiviral sorivudine and fluorouracil , resulting from inhibition of dihydropyrimidine dehydrogenase by sorivudine or chemically related analogues. Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.

4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting.

Alopecia may be seen in a substantial number of cases, particularly females, but is reversible. Other side effects include dermatitis, pigmentation, changes in nails, ataxia and fever.

There have been reports of chest pain, tachycardia, breathlessness and E.C.G. changes after administration of Fluorouracil. Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.

Leucopenia is common and the precautions described above should be followed.

Systemic fluorouracil treatment has been associated with various types of ocular toxicity.

A transient reversible cerebellar syndrome has been reported following fluorouracil treatment. Rarely, a reversible confusional state may occur. Cases of leucoencephalopathy have also been reported.

Additionally, several other reports have been noted including:

Incidences of excessive lacrimation, dacryostenosis, visual changes and photophobia.

Palmar-Plantar Erythrodysesthesia Syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.

Thrombophlebitis / Vein Tracking.

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under "Other Undesirable Effects" and "Special Warnings and Precautions".

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01B C02, Pyrimidine Analogue

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

5.2 Pharmacokinetic properties

After intravenous administration, fluorouracil is distributed through the body water and disappears from the blood within three hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil ready enters the C.S.F and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependent. Following a single intravenous dose of fluorouracil approximately 15% of the dose is excreted unchanged in the urine within six hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Preclinical information has not been included because the toxicity profile of fluorouracil has been established after many years of clinical use. Please refer to section four.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Fluorouracil is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, other anthracyclines and possibly methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

6.3 Shelf life

24 months

After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4 Special precautions for storage

Unopened: Do not store above 25°C
After dilution: Do not store above 25°C (see 6.3 Shelf Life).

Chemical and physical in use stability of fluorouracil solutions with a concentration of 0.35mg/ml and 15.0mg/ml prepared in glucose 5% or sodium chloride 0.9% has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Packs* of one, five or ten Type I colourless glass 10ml vials stoppered with a halobutyl stopper sealed with an aluminium cap.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Cytotoxic Handling Guidelines

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Fluorouracil injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with a absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

Preparation Guidelines

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal

Syringes, vials and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Diluents

Fluorouracil injection may be diluted with glucose 5% injection or sodium chloride 0.9% injection or water for injections immediately before parenteral use.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20851/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2006

10 DATE OF REVISION OF THE TEXT

19/09/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 50 mg of fluorouracil.

Each vial contains 1000mg of fluorouracil in 20ml of solution

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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, either as a single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend 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 one gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight should be used as the basis for the calculation. Reduction of the dose is advisable in patients with any of the following:

1) Cachexia

2) Major surgery within preceding 30 days

3) Reduced bone marrow function

4) Impaired hepatic or renal function

Fluorouracil injection can be given by intravenous injection or, intravenous or intra-arterial infusion.

Adult Dose:

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: 15mg/kg bodyweight but not more than 1g per infusion, diluted in 300 - 500ml of 5% glucose or 9% sodium chloride injection and given by intravenous infusion at a rate of 40 drops per minute over four 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 - 15g has been reached.

Intravenous Injection: l2mg/kg bodyweight may be given daily for three days and then, if there is no evidence of toxicity, 6mg/kg on alternate days for three further doses. An alternative regimen is 15mg/kg as a single intravenous injection once a week throughout the course.

Intra-arterial Infusion: 5/7.5mg/kg 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 four to six weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5-15mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1g daily. A more recent alternative method is to give 15mg/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 fluorouracil 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 fluorouracil should be used.

Children:

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

Elderly:

Fluorouracil should be used in the elderly with similar considerations as with normal adult dosages.

4.3 Contraindications

Fluorouracil is contraindicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Fluorouracil should not be used in the management of non-malignant disease.

4.4 Special warnings and precautions for use

It is recommended that fluorouracil be given only by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites.

All patients should be admitted to hospital for initial treatment.

Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C) count commonly being observed between the seventh and fourteenth day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the thirtieth 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 $2000mm^3$, 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.

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the G.I. tract or haemorrhage at any site. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken therefore, in the selection of patients and adjustment of dosage.

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of fluorouracil. Care should be therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

There have been reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD).

4.5 Interaction with other medicinal products and other forms of interaction

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil - common drugs include methotrexate, metronidazole, leucovorin as well as allopurinol and cimetidine which can affect the availability of the active drug.

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

A clinically significant interaction has been reported between the antiviral sorivudine and fluorouracil , resulting from inhibition of dihydropyrimidine dehydrogenase by sorivudine or chemically related analogues. Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.

4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting.

Alopecia may be seen in a substantial number of cases, particularly females, but is reversible. Other side effects include dermatitis, pigmentation, changes in nails, ataxia and fever.

There have been reports of chest pain, tachycardia, breathlessness and E.C.G. changes after administration of Fluorouracil. Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.

Leucopenia is common and the precautions described above should be followed.

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Thrombophlebitis / Vein Tracking.

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under "Other Undesirable Effects" and "Special Warnings and Precautions".

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L01B C02, Pyrimidine Analogue

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

5.2 Pharmacokinetic properties

After intravenous administration, fluorouracil is distributed through the body water and disappears from the blood within three hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil ready enters the C.S.F and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependent. Following a single intravenous dose of fluorouracil approximately 15% of the dose is excreted unchanged in the urine within six hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Preclinical information has not been included because the toxicity profile of fluorouracil has been established after many years of clinical use. Please refer to section four.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Fluorouracil is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, other anthracyclines and possibly methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

6.3 Shelf life

24 months

After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4 Special precautions for storage

Unopened: Do not store above 25°C
After dilution: Do not store above 25°C (see 6.3 Shelf Life).

Chemical and physical in use stability of fluorouracil solutions with a concentration of 0.35mg/ml and 15.0mg/ml prepared in glucose 5% or sodium chloride 0.9% has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Packs* of one, five or ten Type I colourless glass 20ml vials stoppered with a halobutyl stopper sealed with an aluminium cap.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Cytotoxic Handling Guidelines

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Fluorouracil injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with a absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

Preparation Guidelines

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal

Syringes, vials and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Diluents

Fluorouracil injection may be diluted with glucose 5% injection or sodium chloride 0.9% injection or water for injections immediately before parenteral use.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20851/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2006

10 DATE OF REVISION OF THE TEXT

19/09/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50mg/ml Solution for Injection or Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 50 mg of fluorouracil.

Each vial contains 5000mg of fluorouracil in 100ml of solution

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

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, either as a single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend 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 one gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight should be used as the basis for the calculation. Reduction of the dose is advisable in patients with any of the following:

1) Cachexia

2) Major surgery within preceding 30 days

3) Reduced bone marrow function

4) Impaired hepatic or renal function

Fluorouracil injection can be given by intravenous injection or, intravenous or intra-arterial infusion.

Adult Dose:

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: 15mg/kg bodyweight but not more than 1g per infusion, diluted in 300 - 500ml of 5% glucose or 9% sodium chloride injection and given by intravenous infusion at a rate of 40 drops per minute over four 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 - 15g has been reached.

Intravenous Injection: l2mg/kg bodyweight may be given daily for three days and then, if there is no evidence of toxicity, 6mg/kg on alternate days for three further doses. An alternative regimen is 15mg/kg as a single intravenous injection once a week throughout the course.

Intra-arterial Infusion: 5/7.5mg/kg 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 four to six weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5-15mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1g daily. A more recent alternative method is to give 15mg/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 fluorouracil 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 fluorouracil should be used.

Children:

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

Elderly:

Fluorouracil should be used in the elderly with similar considerations as with normal adult dosages.

4.3 Contraindications

Fluorouracil is contraindicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Fluorouracil should not be used in the management of non-malignant disease.

4.4. Special warnings and precautions for use

It is recommended that fluorouracil be given only by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites.

All patients should be admitted to hospital for initial treatment.

Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C) count commonly being observed between the seventh and fourteenth day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the thirtieth 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 $2000mm^3$, 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.

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There have been reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD).

4.5. Interaction with other medicinal products and other forms of interaction

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4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting.

Alopecia may be seen in a substantial number of cases, particularly females, but is reversible. Other side effects include dermatitis, pigmentation, changes in nails, ataxia and fever.

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Thrombophlebitis / Vein Tracking.

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under "Other Undesirable Effects" and "Special Warnings and Precautions".

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: L01B C02, Pyrimidine Analogue

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

5.2 Pharmacokinetic properties

After intravenous administration, fluorouracil is distributed through the body water and disappears from the blood within three hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil ready enters the C.S.F and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependent. Following a single intravenous dose of fluorouracil approximately 15% of the dose is excreted unchanged in the urine within six hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Preclinical information has not been included because the toxicity profile of fluorouracil has been established after many years of clinical use. Please refer to section four.

6 PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium hydroxide (for pH adjustment)
Water for injections

6.2. Incompatibilities

Fluorouracil is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, other anthracyclines and possibly methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

6.3 Shelf life

24 months

After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4 Special precautions for storage

Unopened: Do not store above 25°C
After dilution: Do not store above 25°C (see 6.3 Shelf Life).

Chemical and physical in use stability of fluorouracil solutions with a concentration of 0.35mg/ml and 15.0mg/ml prepared in glucose 5% or sodium chloride 0.9% has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Packs* of one, five or ten Type I colourless glass 20ml vials stoppered with a halobutyl stopper sealed with an aluminium cap.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Cytotoxic Handling Guidelines

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Fluorouracil injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with an absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

Preparation Guidelines

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

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c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal

Syringes, vials and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Diluents

Fluorouracil injection may be diluted with glucose 5% injection or sodium chloride 0.9% injection or water for injections immediately before parenteral use.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20851/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2006

10 DATE OF REVISION OF THE TEXT

19/09/2006

Patient Information Leaflet

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 20851/0010
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PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluorouracil 50mg/ml Solution for Injection or Infusion

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION IS AND WHAT IT IS USED FOR

Fluorouracil belongs to a group of medicines known as cytotoxics, which are used in the treatment of cancer.

Fluorouracil is usually used to treat breast cancer and colon cancer. However, it may also be given to treat other types of cancer.

2. BEFORE YOU USE FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

Do not use Fluorouracil 50mg/ml Solution for Injection or Infusion

- if you are allergic to fluorouracil or any of the other ingredients
- if you are weakened after a long illness
- if your bone marrow has been damaged by other cytotoxic drugs or radiotherapy
- if you are pregnant, breast-feeding or trying for a baby
- if you have a tumour that is not malignant

Take special care with Fluorouracil 50mg/ml Solution for Injection or Infusion

Your doctor will take special care when giving you fluorouracil:

- if you have a low white blood cell count (you will have blood tests to check this)
- if you have liver or kidney problems
- if you have jaundice (yellowing of the skin)
- if you have angina or a history of heart disease (you should let your doctor know if you experience chest pain while you are receiving your treatment)
- if you have been told by your doctor that you have a low level of the enzyme dihydropyrimidine dehydrogenase (DPD)

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Your doctor will also check your blood before, during and after every treatment. If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking or being given another medicine while you are receiving fluorouracil can affect how it or the other medicine works. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those you may have bought yourself without a prescription. Please check with your doctor if you are taking any of the following (or any other medication):

- Methotrexate, another cytotoxic drug
- Metronidazole, an antibiotic
- Calcium leucoverin (calcium folinate), used to reduce the harmful effects of cytotoxic drugs
- Allopurinol, used to treat gout
- Cimetidine, used to treat stomach ulcers
- Warfarin, used to treat blood clots
- Sorivudine, an antiviral drug

Pregnancy

Fluorouracil should not be given to you if you are pregnant, because it can cause serious birth defects.

Female patients should also avoid getting pregnant while being treated with fluorouracil and for at least six months afterwards. Male patients receiving fluorouracil should take adequate precautions to ensure that their partner does not become pregnant for the same period. If you are considering becoming parents after the treatment, you should discuss this with your doctor.

Men who wish to father children in the future should seek advice about freezing sperm before the fluorouracil treatment is started.

Breast-feeding

Fluorouracil should not be given to you if you are breast-feeding, as fluorouracil might pass into breast milk and affect the baby.

Driving and using machines:

Fluorouracil treatment should not affect your ability to drive, but if you feel unwell, you should not drive or operate machinery.

3. HOW TO USE FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

Fluorouracil injection can be given by intravenous injection (the solution is given directly into a vein) or, intravenous or intra-arterial infusion (the solution is diluted and given by a drip into a vein or artery).

Fluorouracil 50mg/ml Solution for Injection or Infusion will only be given to you under the supervision of a doctor specialised in this type of treatment, which should be started in hospital. It may be diluted with glucose solution, sodium chloride solution or water for injections before use. It is injected into a vein or artery. If it is given into an artery it must be diluted first.

The dosage of fluorouracil depends on the condition you are being treated for, your bodyweight, if you have had recent surgery, how well your liver and kidneys are working and results of your blood tests.

Your general condition and your response to the treatment will be closely observed before, during and after the fluorouracil treatment. This will include blood tests.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluorouracil 50mg/ml Solution for Injection or Infusion can cause side effects, although not everybody gets them.

These include nausea, vomiting, temporary hair loss, skin problems, changes in your nails, feeling unsteady on your feet, quickening of the heart and breathlessness (following injection), painful and watery eyes, changes in vision and sensitivity to light, feeling confused and reddening of the palms of the hands and soles of the feet.

If you develop any of the following symptoms, **tell your doctor immediately:**

- chest pain
- diarrhoea
- blood stained or black bowel motions
- sore throat, sore mouth or mouth ulcers
- feeling generally unwell
- fever
- aching muscles and joints
- weakness,
- confusion
- difficulties with co-ordination, memory, thinking, or talking
- fits
- severe headache

Pain may occur temporarily at the injection site.

Allergic reactions to fluorouracil can occur, with wheezing, a skin rash or swelling of your lips, eyes or tongue. You should contact your doctor **immediately** if you develop such symptoms.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

Keep out of the reach and sight of children.

Do not use Fluorouracil 50mg/ml Solution for Injection or Infusion after the expiry date which is stated on the label or carton. The expiry date refers to the last day of that month.

<o not use Fluorouracil 50mg/ml Solution for Injection or Infusion if you notice signs of discoloration {description of the visible signs of deterioration}.

After first opening or following dilution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What Fluorouracil 50mg/ml Solution for Injection or Infusion contains

- The active substance is fluorouracil
  The other ingredients are sodium hydroxide and water for injections.

What X looks like and contents of the pack

Fluorouracil 50mg/ml Solution for Injection or Infusion is a clear and colourless solution free from particles.

Fluorouracil 50mg/ml Solution for Injection or Infusion is available in single packs containing:-

- 250mg of fluorouracil in 5ml of solution
- 500mg of fluorouracil in 10ml of solution
- 1000mg of fluorouracil in 20ml of solution
- 5000mg of fluorouracil in 100ml of solution

Marketing Authorisation Holder and Manufacturer

Fluorouracil 50mg/ml Solution for Injection or Infusion is manufactured by:-

EBEWE Pharma
Ges.m.b.H. Nfg. KG, A-4866
Unterach
Austria

for the Marketing Authorisation holder

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF

This leaflet was last approved on .....

Labels/Packaging

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

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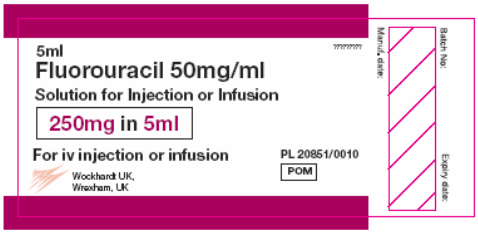


100% size

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

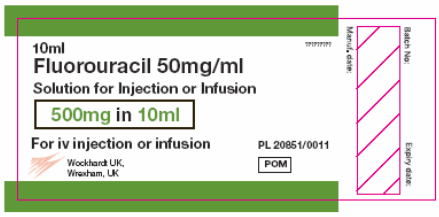
PL 20851/0010

Fluorouracil 50mg/ml
1 Vial
(250mg in 5ml)
Colour: Red 221, Black

Mock-up 07/07/06

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 20851/0011



100% size

Fluorouracil 50mg/ml
1 Vial
(500mg in 10ml)
Colour: Green 370, Black

Mock-up 29/06/06

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

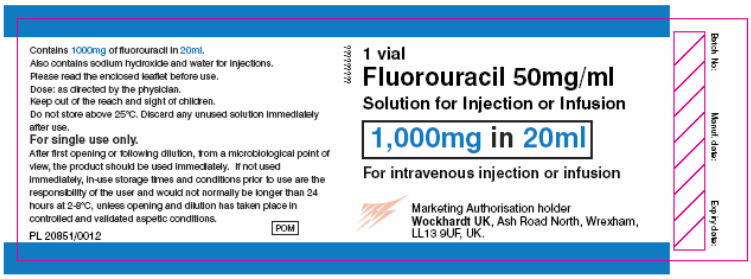
PL 20851/0011

Fluorouracil 50mg/ml
1 Vial
(500mg in 10ml)
Colour: Green 370, Black

Mock-up 07/07/06

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 20851/0012



100%

Fluorouracil 50mg/ml
1 Vial
(1000mg in 20ml)
Colour: Blue 285, Black

Mock-up 07/07/06

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 20851/0012

Fluorouracil 50mg/ml
1 Vial
(1000mg in 20ml)
Colour: Blue 285, Black

Mock-up 07/07/06

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 20851/0013

100%

Fluorouracil 50mg/ml
1 Vial
(5000mg in 100ml)
Colour: Red 186, Black

Mock-up 07/07/06

FLUOROURACIL 50MG/ML SOLUTION FOR INJECTION OR INFUSION

PL 20851/0013

Fluorouracil 50mg/ml
1 Vial
(5000mg in 100ml)
Colour: Red 186, Black

Mock-up 07/07/06