Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Levofolinic Acid 10 mg/ml Solution for Injection

UK/H/0926/001/DC
UK licence no: PL 04515/0210

Mayne Pharma Plc

LAY SUMMARY

On 12 February 2008 the MHRA granted Mayne Pharma Plc a Marketing Authorisation (licence) for the medicinal product Levofolinic Acid 10 mg/ml Solution for Injection. This is a prescription only medicine (POM) to be used in combination with anticancer drugs to increase their effects (e.g. 5-flurouracil) or to reduce their harmful effects (e.g. methotrexate).

Levofolinic Acid 10 mg/ml Solution for Injection belongs to a group of drugs known as detoxifying agents for antitumor treatment.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Levofolinic Acid 10 mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Information About Initial Procedure

Product Name	Levofolinic Acid 10 mg/ml Solution for Injection
Type of Application	Generic, Article 10.1
Active Substance	Calcium levofolinate
Form	Solution for injection
Strength	10mg/ml
MA Holder	Mayne Pharma Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW UK
RMS	UK
CMS	Luxemburg, Spain, Belgium and France
Procedure Number	UK/H/0926/001/DC
Timetable	Day 208 – 14 September 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levofolinic Acid 10 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg levofolinic acid (as calcium levofolinate pentahydrate).

Each 2.5, 5, 10 and 17.5 ml vial contains 25, 50, 100 and 175 mg levofolinic acid respectively (as calcium levofolinate pentahydrate).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear yellow to green-yellow solution with pH of 6.5 to 8.5 and osmolarity of 240 to 300 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levofolinic acid is indicated

• to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, this procedure is commonly known as “Folinic Acid Rescue”;

• in combination with 5-fluorouracil in cytotoxic therapy.

4.2 Posology and method of administration

For intravenous and intramuscular administration only. In the case of intravenous administration, no more than 160 mg of levofolinic acid should be injected per minute due to the calcium content of the solution.

For instructions regarding the dilution of the product for intravenous infusion, see Section 6.6.

Levofolinic acid rescue in methotrexate therapy:

Since the levofolinic acid rescue dosage regimen depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of levofolinic acid rescue. Therefore, it is best to

refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of levofolinic acid.

The following guidelines may serve as an illustration of regimens used in adults, elderly and children:

Levofolinic acid rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured.

Dosages above 12.5-25 mg should be given parenterally due to saturable enteral absorption of levofolinic acid.

Levofolinic acid rescue is necessary when methotrexate is given at doses exceeding 500 mg/m² body surface and should be considered with doses of 100 mg – 500 mg/m² body surface.

Dosage and duration of levofolinic acid rescue primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate. As a rule, the first dose of levofolinic acid is 7.5 mg (3-6 mg/m²) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched over to the oral form.

In addition to levofolinic acid administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the levofolinic acid rescue treatment. Renal function should be monitored through daily measurements of serum creatinine.

Forty-eight hours after the start of the methotrexate infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level is >0.5 µmol/l, levofolinic acid dosages should be adapted according to the following table:

Residual methotrexate blood level 48 hours after the start of the methotrexate administration:	Additional levofolinic acid to be administered every 6 hours for 48 hours or until levels of methotrexate are lower than 0.05 µmol/l:
> 0.5 µmol/l	7.5 mg/m²
> 1.0 µmol/l	50 mg/m²
> 2.0 µmol/l	100 mg/m²

In combination with 5-fluorouracil in cytotoxic therapy: Different regimens and different dosages are used, without any dosage having been proven to be the optimal one.

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

Bimonthly regimen: Levofolinic acid 100 mg/m² by intravenous infusion over two hours, followed by bolus 400 mg/m² of 5-FU and 22-hour infusion of 5-FU (600 mg/m²) for 2 consecutive days, every 2 weeks on days 1 and 2.

Weekly regimen: Levofolinic acid 10 mg/m² by bolus i.v. injection or 100 to 250 mg/m² as i.v. infusion over a period of 2 hours plus 500 mg/m² 5-fluorouracil as i.v. bolus injection in the middle or at the end of the levofolinic acid infusion.

Monthly regimen: Levofolinic acid 10 mg/m² by bolus i.v. injection or 100 to 250 mg/m² as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as i.v. bolus injection during five consecutive days.

For the combination therapy with 5-fluorouracil, modification of the 5-fluorouracil dosage and the treatment-free interval may be necessary depending on patient condition, clinical response and dose limiting toxicity as stated in the product information of 5-fluorouracil. A reduction of levofolinic acid dosage is not required.

The number of repeat cycles used is at the discretion of the clinician.

Antidote to the folic acid antagonists trimetrexate, trimethoprim, and pyrimethamine:

Trimetrexate toxicity:

• Prevention: Levofolinic acid should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Levofolinic acid can be administered either by the intravenous route at a dose of 10 mg/m² for 5 to 10 minutes every 6 hours for a total daily dose of 40 mg/m², or by oral route with four doses of 10 mg/m² administered at equal time intervals. Daily doses of levofolinic acid should be adjusted depending on the haematological toxicity of trimetrexate.

• Overdosage (possibly occurring with trimetrexate doses above 90 mg/m² without concomitant administration of levofolinic acid): after stopping trimetrexate, levofolinic acid 20 mg/m² IV every 6 hours for 3 days.

Trimethoprim toxicity:

• After stopping trimethoprim, 1.5-5 mg/day levofolinic acid until recovery of a normal blood count.

Pyrimethamine toxicity:

• In case of high dose pyrimethamine or prolonged treatment with low doses, levofolinic acid 2.5 to 25 mg/day should be simultaneously administered, based on the results of the peripheral blood counts.

4.3 Contraindications

• Known hypersensitivity to levofolinic acid, or to any of the excipients.

• Pernicious anaemia or other anaemias due to vitamin B12 deficiency.

Regarding the use of levofolinic acid with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6, “Pregnancy and Lactation” and the summaries of product characteristics for methotrexate and 5-fluorouracil containing medicinal products.

4.4 Special warnings and precautions for use

Levofolinic acid should only be given by intramuscular or intravenous injection and must not be administered intrathecally.

When folinic acid has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported.

General

Levofolinic acid should be used with methotrexate or 5-fluorouracil only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Levofolinic acid treatment may mask pernicious anaemia and other anaemias resulting from vitamin B12 deficiency.

Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mecaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

In epileptic patients treated with phenobarbital, phenytoin, primidone, and succinimides there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during levofolinic acid administration and after discontinuation is recommended (see also section 4.5 Interactions).

Levofolinic acid/5-fluorouracil

Levofolinic acid may enhance the toxicity risk of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. When levofolinic acid and 5-fluorouracil are used in combination, the 5-fluorouracil dosage has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone.

Combined 5-fluorouracil/levofolinic acid treatment should neither be initiated nor maintained in patients with symptoms of gastrointestinal toxicity, regardless of the severity, until all of these symptoms have completely disappeared.

Because diarrhoea may be a sign of gastrointestinal toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of 5-FU until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities. Therefore, particular care should be taken when treating these patients.

In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of 5-fluorouracil.

Levofolinic acid must not be mixed with 5-fluorouracil in the same IV injection or infusion.

Calcium levels should be monitored in patients receiving combined 5-fluorouracil/levofolinic acid treatment and calcium supplementation should be provided if calcium levels are low.

Levofolinic acid/methotrexate

For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate.

Levofolinic acid has no effect on non-haematological toxicities of methotrexate such as the nephrotoxicity resulting from methotrexate and/or metabolite precipitation in the kidney. Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure and all toxicities associated with methotrexate (please refer to the SPC for methotrexate). The presence of preexisting or methotrexate induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of levofolinic acid.

Excessive levofolinic acid doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where levofolinic acid accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport implies also resistance to folinic acid rescue as both medicinal products share the same transport system.

An accidental overdose with a folate antagonist, such as methotrexate, should be treated as a medical emergency. As the time interval between methotrexate administration and levofolinic acid rescue increases, levofolinic acid effectiveness in counteracting toxicity decreases.

The possibility that the patient is taking other medications that interact with methotrexate (eg, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

4.5 Interaction with other medicinal products and other forms of interaction

When levofolinic acid is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.

Levofolinic acid may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see also sections 4.4 and 4.8).

Concomitant administration of levofolinic acid with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil (see sections 4.2, 4.4 and 4.8).

4.6 Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. No formal animal reproductive toxicity studies with levofolinic acid have been conducted. There are no indications that folic acid induces harmful effects if administered during pregnancy. During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of levofolinic acid to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of levofolinic acid with 5-fluorouracil. Please refer also to the Summaries of Product Characteristics for methotrexate, other folate antagonists and 5-fluorouracil containing medicinal products.

Lactation

It is not known whether levofolinic acid is excreted into human breast milk. Levofolinic acid can be used during breast feeding when considered necessary according to the therapeutic indications.

4.7 Effects on ability to drive and use machines

Levofolinic acid has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Both therapeutic indications:

Immune system disorders

Very rare (<0.01%): allergic reactions, including anaphylactoid reactions and urticaria.

Psychiatric disorders

Rare (0.01-0.1%): insomnia, agitation and depression after high doses.

Gastrointestinal disorders

Rare (0.01-0.1%): gastrointestinal disorders after high doses.

Neurological disorders

Rare (0.01-0.1%): increase in the frequency of attacks in epileptics (see also section 4.5).

General disorders and administration site conditions

Uncommon (0.1-1%): fever has been observed after administration of levofolinic acid as solution for injection.

Combination therapy with 5-fluorouracil:

Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities:

Monthly regimen:

Gastrointestinal disorders

Very common (>10%): vomiting and nausea

General disorders and administration site conditions

Very common (>10%): (severe) mucosal toxicity.

No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity).

Weekly regimen:

Gastrointestinal disorders

Very common (>10%): diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more levofolinic acid than the recommended dosage. However, excessive amounts of levofolinic acid may nullify the chemotherapeutic effect of folic acid antagonists.

Should overdosage of the combination of 5-fluorouracil and levofolinic acid occur, the overdosage instructions for 5-FU should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment

ATC code: V03AF03

Levofolinic acid is the active l-isomer of 5-formyl tetrahydrofolic acid (folinic acid) and an essential coenzyme for nucleic acid synthesis in cytotoxic therapy.

Levofolinic acid is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Levofolinic acid and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. It also protects cells from the effects of folate antagonist by repletion of the reduce folate pool. Levofolinic acid serves as a pre-reduced source of H4 folate; it can therefore bypass folate antagonist blockage and provide a source for the various coenzyme forms of folic acid.

Levofolinic acid is also frequently used in the biochemical modulation of fluoropyridine (5-FU) to enhance its cytotoxic activity. 5-FU inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and levofolinic acid enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5FU-TS complex and increasing activity.

Finally intravenous levofolinic acid can be administered for the prevention and treatment of folate deficiency when it cannot be prevented or corrected by the administration of folic acid by the oral route. This may be the case during total parenteral nutrition and severe malabsorption disorders. It is also indicated for the treatment of megaloblastic anaemia due to folic acid deficiency, when oral administration is not feasible.

5.2 Pharmacokinetic properties

Absorption

Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels (Cmax) are achieved.

Metabolism

Levofolinic acid (L-5-formyl-tetrahydrofolate, L-5-formyl-THF), is the active enantiomer of folinic acid.

The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and intestinal mucosa.

Distribution

The distribution volume of folinic acid is not known.

Peak serum levels of the parent substance (L-5-formyl-tetrahydrofolic acid, folinic acid) are reached 10 minutes after i.v. administration.

AUC for L-5-formyl-THF and 5-methyl-THF were 28.4±3.5 mg.min/l and 129±112 mg.min/l after a dose of 25 mg.

Elimination

The elimination half-life for levofolinic acid is 32 - 35 minutes.

The total terminal half-life of the active metabolites is about 6 hours (after intravenous and intramuscular administration).

Excretion

80-90 % with the urine (5- and 10-formyl-tetrahydrofolates inactive metabolites), 5-8 % with the faeces.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Water for Injections

Hydrochloric Acid (as a pH adjuster)

Sodium Hydroxide (as a pH adjuster)

6.2 Incompatibilities

Incompatibilities have been reported between injectable forms of folinic acid and injectable forms of droperidol, fluorouracil, foscarnet and methotrexate.

Droperidol

1. Droperidol 1.25 mg/0.5 ml with folinic acid 5 mg/0.5 ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25° C followed by 8 minutes of centrifugation.

2. Droperidol 2.5 mg/0.5 ml with folinic acid 10 mg/0.5 ml, immediate precipitation when the drugs were injected sequentially into a Y-site without flushing the Y-side arm between injections.

Fluorouracil

Levofolinic acid must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/ml with levofolinic acid 20 mg/ml, with or without dextrose 5% in water, has been shown to be incompatible when mixed in different amounts and stored at 4 °C, 23 °C, or 32 °C in polyvinyl chloride containers.

Foscarnet

Foscarnet 24 mg/ml with folinic acid 20 mg/ml formation of a cloudy yellow solution reported.

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

18 months

Following dilution with the recommended infusion fluids, chemical and physical in-use stability has been demonstrated when protected from light for up to 24 hours at 2-8ºC. In addition, following dilution with sodium chloride 0.9% and glucose 5 %, chemical and physical in-use stability has been demonstrated when protected from light for up to 24 hours 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 when stored at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions. Because of the risk of degradation, diluted solutions should be protected from light prior to use if necessary.

6.4 Special precautions for storage

Store at 2 °C – 8 °C (in a refrigerator).

Store in original container to protect from light.

6.5 Nature and contents of container

Type I clear glass vial with chlorobutyl stopper each containing the equivalent of 25 mg, 50 mg, 100 mg or 175mg of levofolinic acid in 2.5 ml, 5 ml, 10 ml or 17.5ml of solution respectively. Packed in cartons of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Prior to administration, levofolinic acid should be inspected visually. The solution for injection or infusion should be a clear and yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded. Levofolinic acid solution for injection or infusion is intended only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

For intravenous infusion, the 175 mg in 17.5 ml Solution for Injection may be diluted with any of the following infusion fluids before use: Sodium Chloride 0.9%; Glucose 5%; Glucose 10%; Glucose 5% and Sodium Chloride 0.9% Injection; Compound Sodium Lactate Injection.

7 MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc

Queensway

Royal Leamington Spa

Warwickshire CV31 3RW

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04515/0210

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/02/2008

10 DATE OF REVISION OF THE TEXT

12/02/2008

Module 3

Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

mayne

Levofolinic Acid
10 mg/ml Solution for Injection

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

In this leaflet:

1. WHAT LEVOFOLINIC ACID SOLUTION FOR INJECTION IS AND WHAT IT IS USED FOR

Levofolinic Acid Solution for Injection contains levofolinic acid, which is a vitamin from the B group.

Levofolinic Acid Solution for Injection may be used in combination with other medicines to reverse their effects. In particular it may be used to reduce the harmful effects of an anti-cancer drug called methotrexate.

Levofolinic Acid Solution for Injection can be used to increase the effect of another drug, 5-fluorouracil, in treating some types of cancer.

2. BEFORE YOU USE LEVOFOLINIC ACID SOLUTION FOR INJECTION

Do not use Levofolinic Acid Solution for Injection:
- if you are allergic (hypersensitive) to levofolinic acid or any of the other ingredients of Levofolinic Acid Solution for Injection
- you have a blood disease called anaemia caused by too little Vitamin B_{12}.

Take special care with Levofolinic Acid Solution for Injection:
- if you are having treatment with methotrexate or 5-fluorouracil. Your doctor will be experienced in cancer treatment.
- if you are suffering from diarrhoea, sore mouth or stomach upset and receiving treatment along with 5-fluorouracil.

Using other medicines

You will not be given levofolinic acid at the same time as receiving other cancer drugs, such as methotrexate, since it may stop them from working properly. Levofolinic Acid Solution for Injection is usually given 12 - 24 hours after starting treatment with methotrexate.

If you are taking other medicines for the treatment of epilepsy (e.g. phenobarbitone, phenytoin, primidone or succinimides) then levofolinic acid may reduce their effects.

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

Pregnancy and breast-feeding

There is no experience of the use of levofolinic acid during pregnancy. Ask your doctor for advice before using levofolinic acid if you are pregnant.

It is not known whether levofolinic acid passes into mothers' milk. Ask your doctor for advice before breast-feeding whilst being treated with levofolinic acid.

When used together with methotrexate or 5-fluorouracil, refer to the product information for these treatments.

Ask your doctor for advice before taking any medicine.

Driving and using machines

Levofolinic Acid Solution for Injection has no known effect on the ability to drive or use machines.

Important information about some of the ingredients of Levofolinic Acid Solution for Injection:

This medicine is available in 4 different vial sizes. The 2.5 ml and 5 ml products contain less than 1 mmol sodium (23 mg) per vial i.e. essentially 'sodium free'.

The 10 ml product contains 1.3 mmol (30 mg) sodium per vial and the 17.5 ml product contains 2.3 mmol (53 mg) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE LEVOFOLINIC ACID SOLUTION FOR INJECTION

A doctor will usually give you the medicine. The dose depends on the nature of your treatment, your age and your medical condition. Your doctor will give you Levofolinic Acid Solution for Injection by injecting it into one of your veins or muscle. If it is given into a vein it can be given as an injection or via a drip (infusion). Levofolinic Acid Solution for Injection will not be given by any other route.

When used to reduce the harmful effects of methotrexate, your treatment will usually start 12 - 24 hours after your methotrexate treatment starts. The usual dose of Levofolinic Acid Solution for Injection is 7.5 mg every 6 hours for 72 hours. However, the doctor may decide to change this, depending on your condition and the dose of methotrexate you have already received. During your treatment your doctor may also wish to give you other fluids and to take blood samples from you.

When Levofolinic Acid Solution for Injection is used with 5-Fluorouracil, your treatment will either be given weekly, monthly or twice a month. Your doctor will decide on the best treatment period.

If you use more Levofolinic Acid Solution for Injection than you should

As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much, however if you have any concerns then tell your doctor.

If you miss a dose of Levofolinic Acid Solution for Injection

If you think you have not been given a dose of Levofolinic Acid Solution for Injection, tell your doctor immediately.

If you have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levofolinic Acid Solution for Injection can cause side effects, although not everybody gets them.

A few people can be allergic to some medicines; if any of the following very rare side effects occur soon after having your injection, tell your doctor immediately:

- Sudden chest tightness or wheeziness
- Swelling of eyelids, face or lips
- Skin rash - red spots or hives (skin lumps)
- Collapse

If you are being given Levofolinic Acid Solution for Injection to increase the effect of 5-Fluorouracil or reduce the effects of methotrexate, the following side effects can occur:

Uncommon (occurs in between 1 in 1000 and 1 in 100 people):

- fever

Rare (occurs in between 1 in 1000 and 1 in 10,000 people):

- sleeplessness,
- feeling anxious or depressed after high doses,
- upset stomach after high doses,
- an increase in the number of fits if you are epileptic.

If you are being given Levofolinic Acid Solution for Injection to increase the effect of 5-Fluorouracil, the following side effects can occur:

If you are being given Levofolinic Acid Solution for Injection and 5-Fluorouracil each month:

Very common (occurs in more than 1 in 10 people):

- feeling or being sick,
- sore mouth or lips.

If you are being given Levofolinic Acid Solution for Injection and 5-Fluorouracil each week:

Very common (occurs in more than 1 in 10 people):

- diarrhoea,
- dehydration (loss of fluids usually accompanied by severe thirst, often with dizziness, dry loose skin and sunken features, especially the eyes).

If you experience diarrhoea or dehydration, you may require medical treatment. In some cases, these side effects may be life-threatening or fatal.

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

5. HOW TO STORE LEVOFOLINIC ACID SOLUTION FOR INJECTION

Keep out of the reach and sight of children.

Do not use Levofolinic Acid Solution for Injection after the expiry date which is stated on the label or carton.

Store in a refrigerator (2 - 8°C).

Keep the vials in the outer carton in order to protect from light.

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 Levofolinic Acid Solution for Injection contains

- The active substance is levofolinic acid (as the calcium salt). 1 ml of solution contains 10 mg of levofolinic acid.
- The other ingredients are sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

What Levofolinic Acid Solution for Injection looks like and contents of the pack

Levofolinic Acid Solution for Injection is a clear pale yellow solution for injection.

One vial of 2.5 ml of solution contains 25 mg of levofolinic acid, one vial of 5 ml of solution contains 50 mg of levofolinic acid, one vial of 10 ml of solution contains 100 mg of levofolinic acid and one vial of 17.5 ml of solution contains 175 mg of levofolinic acid. Each carton contains one vial. Not all pack sizes may be marketed.

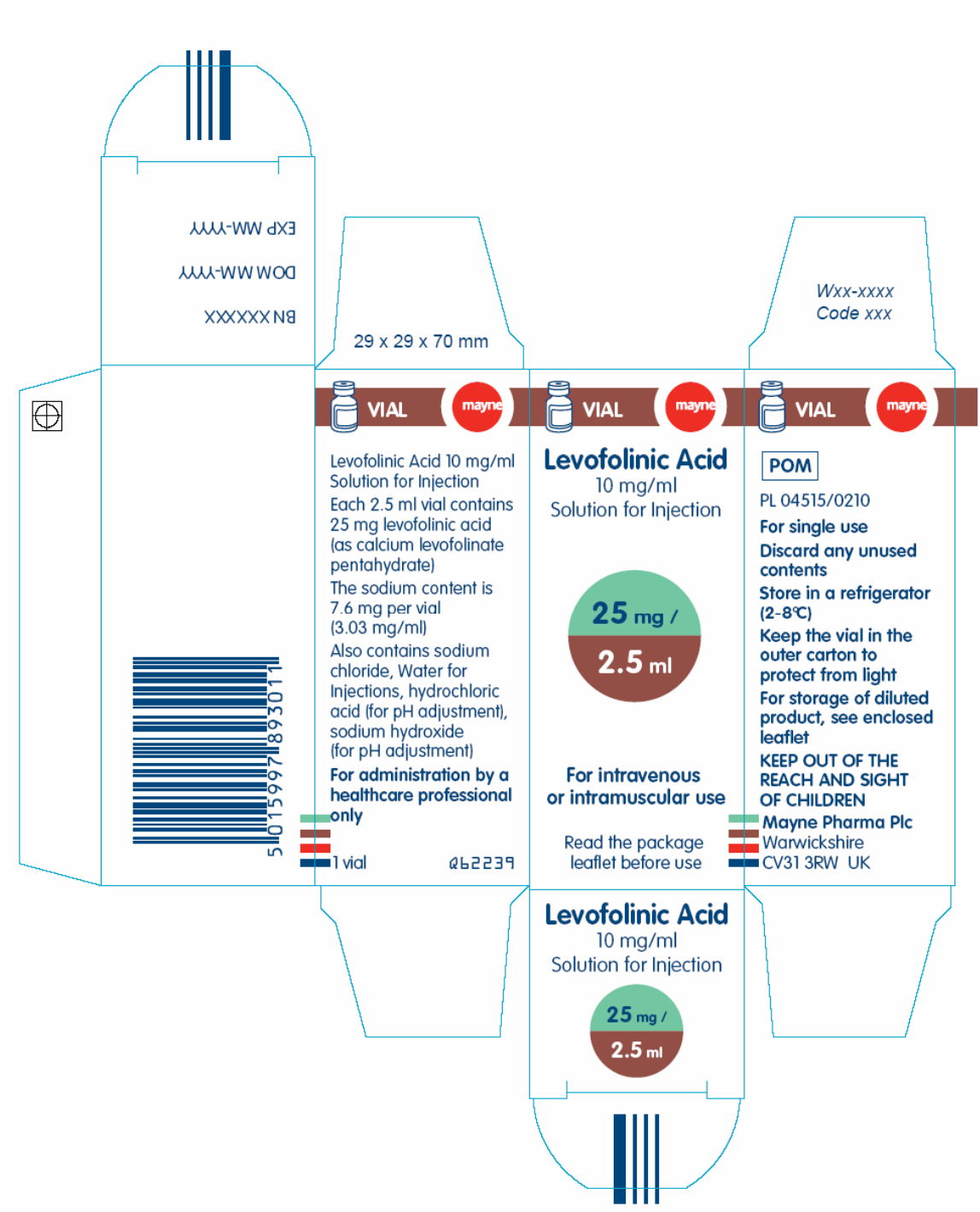
Marketing Authorisation Holder and Manufacturer

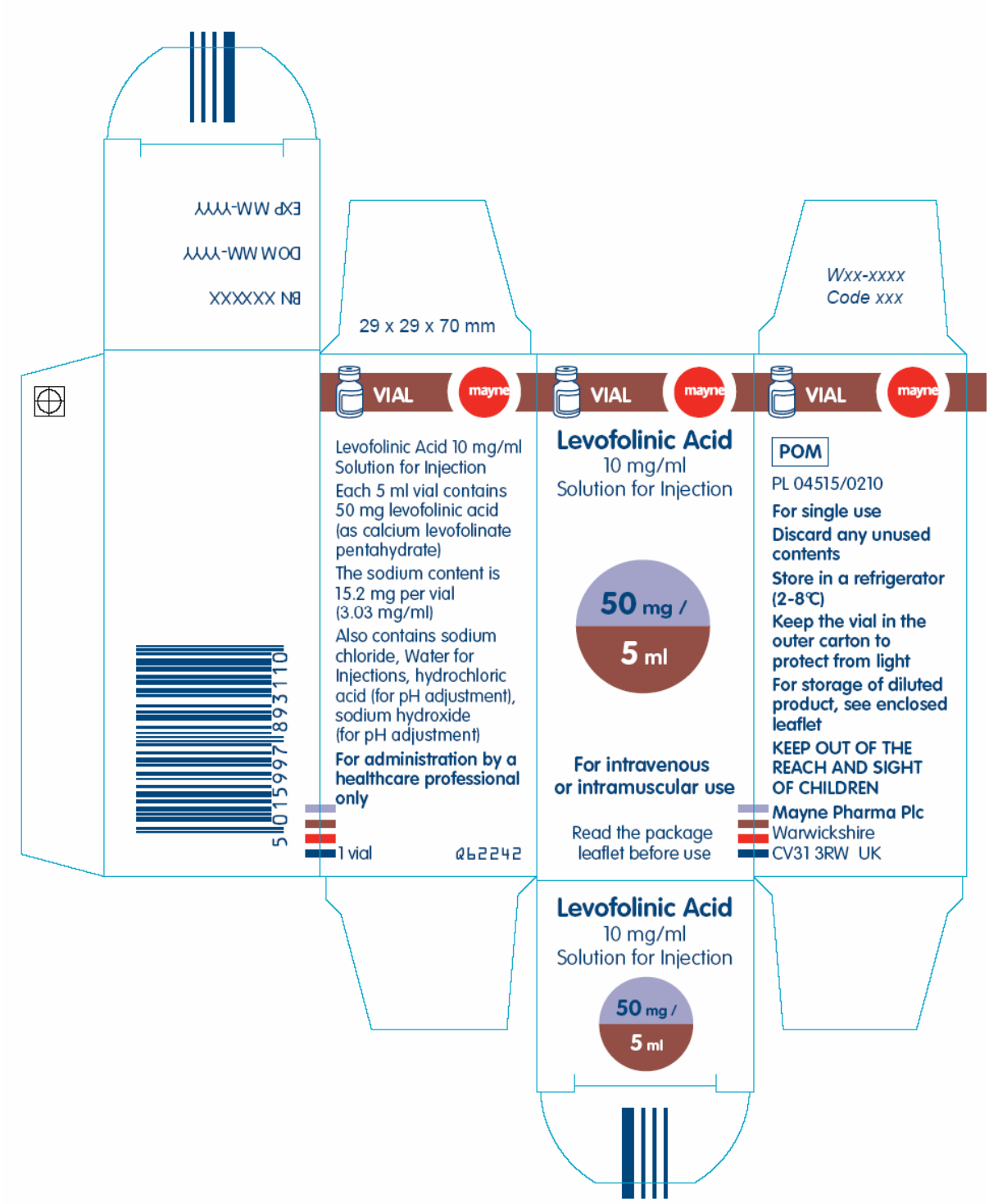
The Marketing Authorisation Holder is: Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, UK.

The manufacturer is Wasserburger Arzneimittelwerk GmbH, 83512 Wasserburg, Germany (a Mayne Pharma company).

This leaflet was last approved in 09/2007.

Module 4
Labelling

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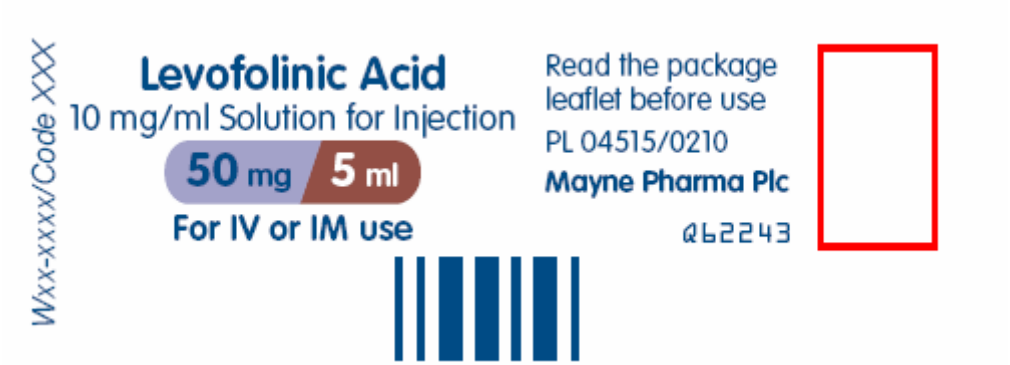
Code xxx
VIAL
mayne
VIAL
mayne
VIAL
mayne
Levofolinic Acid 10 mg/ml Solution for Injection
Each 5 ml vial contains 50 mg levofolinic acid (as calcium levofolinate pentahydrate)
The sodium content is 15.2 mg per vial (3.03 mg/ml)
Also contains sodium chloride, Water for Injections, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment)
For administration by a healthcare professional only
1 vial
Q62242
5 015997 893110
Levofolinic Acid
10 mg/ml
Solution for Injection
50 mg / 5 ml
For intravenous or intramuscular use
Read the package leaflet before use
POM
PL 04515/0210
For single use
Discard any unused contents
Store in a refrigerator (2-8°C)
Keep the vial in the outer carton to protect from light
For storage of diluted product, see enclosed leaflet
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Warwickshire
CV31 3RW UK
Levofolinic Acid
10 mg/ml
Solution for Injection
50 mg / 5 ml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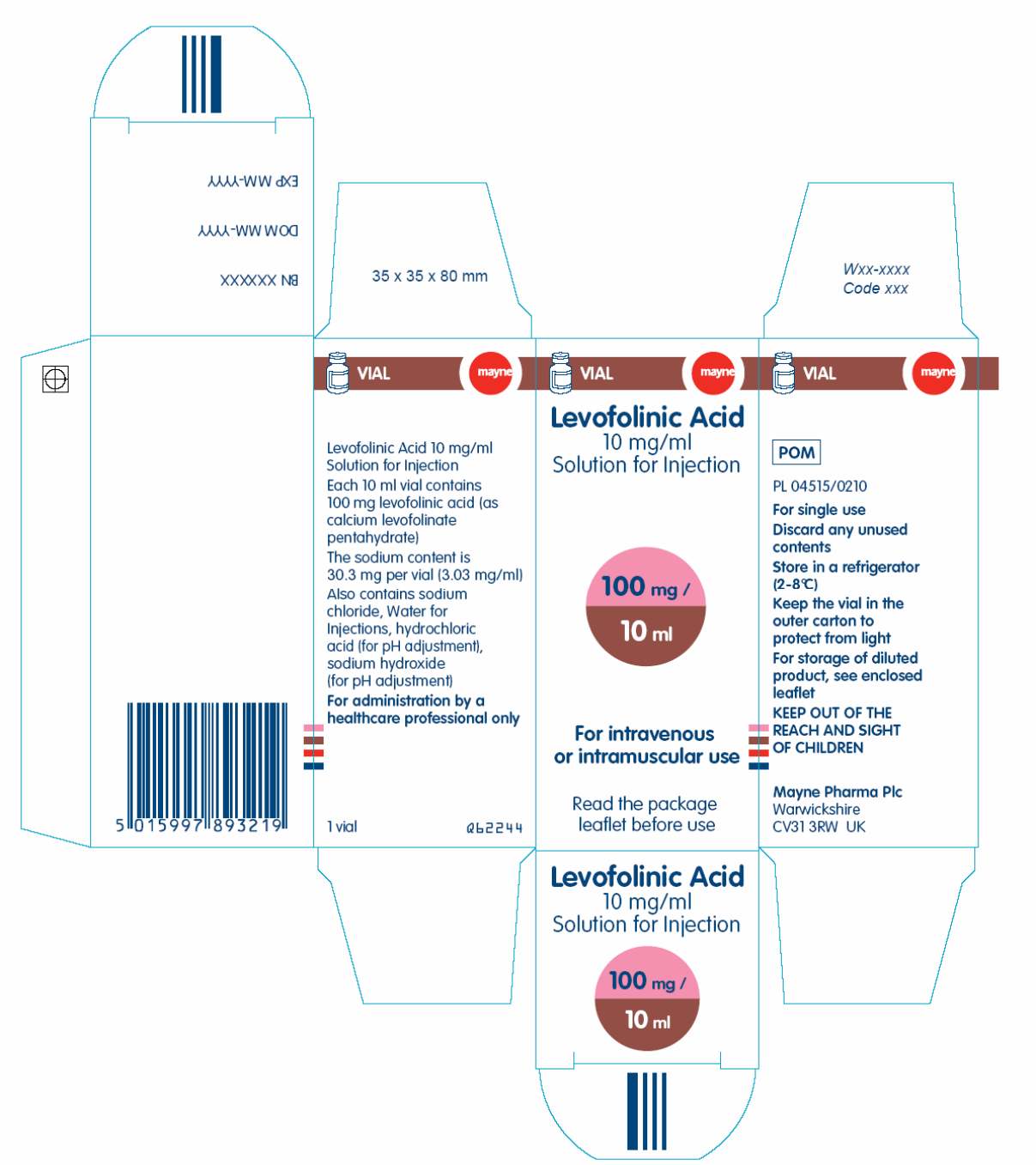
Levofolinic Acid
10 mg/ml Solution for Injection
50 mg 5 ml
For IV or IM use
Read the package leaflet before use
PL 04515/0210
Mayne Pharma Plc
Q62243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DOM MM-YYYY
BN XXXXXX
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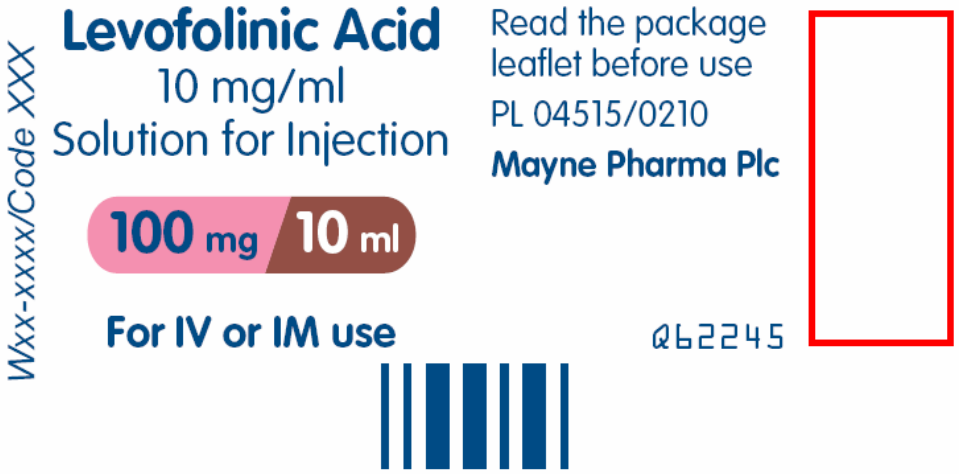
Wxx-xxxx
Code xxx
VIAL
mayne
Levofolinic Acid 10 mg/ml Solution for Injection
Each 10 ml vial contains 100 mg levofolinic acid (as calcium levofolinate pentahydrate)
The sodium content is 30.3 mg per vial (3.03 mg/ml)
Also contains sodium chloride, Water for Injections, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment)
For administration by a healthcare professional only
5 015997 893219
1 vial
Q62244
Levofolinic Acid
10 mg/ml
Solution for Injection
100 mg / 10 ml
For intravenous or intramuscular use
Read the package leaflet before use
POM
PL 04515/0210
For single use
Discard any unused contents
Store in a refrigerator (2-8°C)
Keep the vial in the outer carton to protect from light
For storage of diluted product, see enclosed leaflet
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Warwickshire
CV31 3RW UK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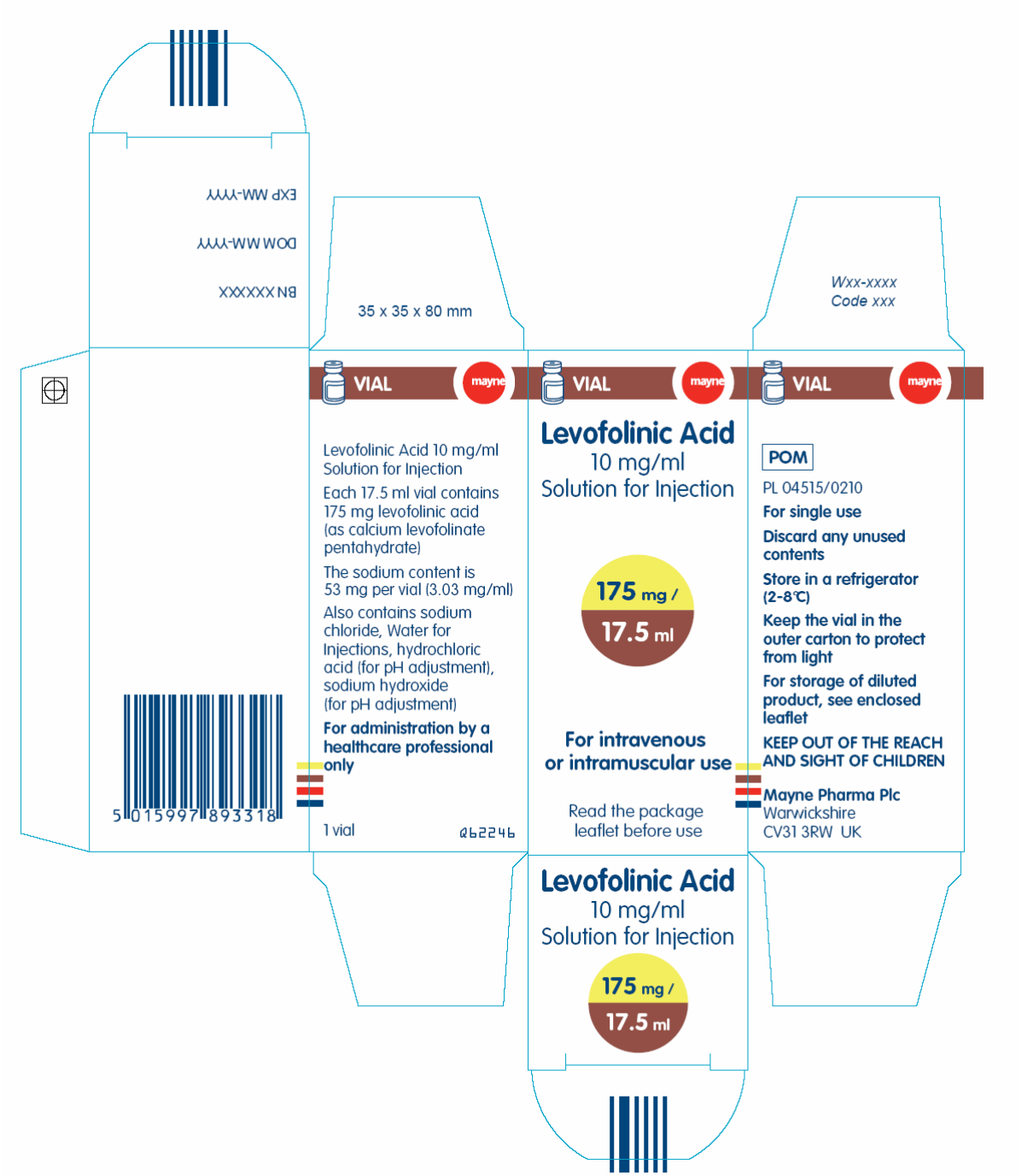
Levofolinic Acid
10 mg/ml
Solution for Injection
100 mg 10 ml
For IV or IM use
Read the package leaflet before use
PL 04515/0210
Mayne Pharma Plc
Q62245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DOM MM-YYYY
BN XXXXXX
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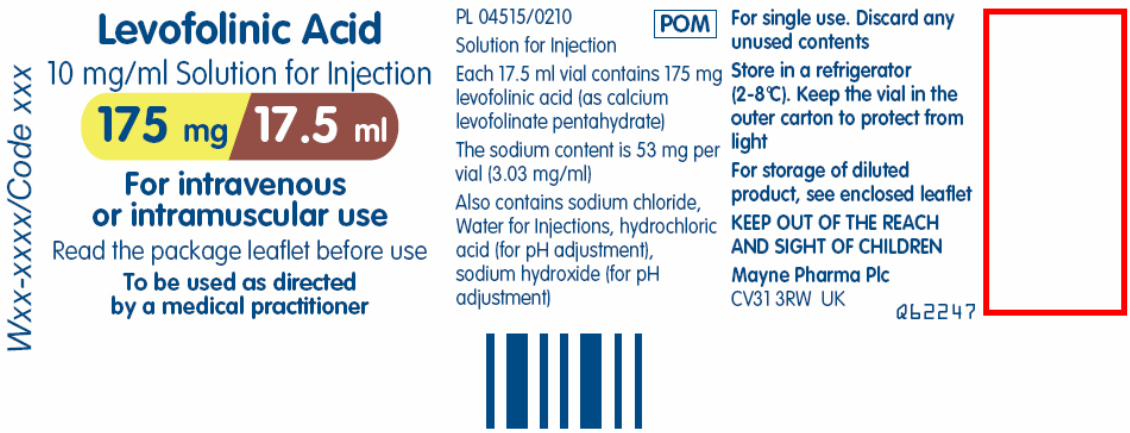
Wxx-xxxx
Code xxx
VIAL
mayne
Levofolinic Acid 10 mg/ml Solution for Injection
Each 17.5 ml vial contains 175 mg levofolinic acid (as calcium levofolinate pentahydrate)
The sodium content is 53 mg per vial (3.03 mg/ml)
Also contains sodium chloride, Water for Injections, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment)
For administration by a healthcare professional only
1 vial
Q62246
5 015997 893318
Levofolinic Acid
10 mg/ml
Solution for Injection
175 mg / 17.5 ml
For intravenous or intramuscular use
Read the package leaflet before use
POM
PL 04515/0210
For single use
Discard any unused contents
Store in a refrigerator (2-8°C)
Keep the vial in the outer carton to protect from light
For storage of diluted product, see enclosed leaflet
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Warwickshire
CV31 3RW UK


Wxx-xxxx/Code xxx
Levofolinic Acid
10 mg/ml Solution for Injection
175 mg / 17.5 ml
For intravenous or intramuscular use
Read the package leaflet before use
To be used as directed by a medical practitioner
PL 04515/0210
POM
Solution for Injection
Each 17.5 ml vial contains 175 mg levofolinic acid (as calcium levofolinate pentahydrate)
The sodium content is 53 mg per vial (3.03 mg/ml)
Also contains sodium chloride, Water for Injections, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment)
For single use. Discard any unused contents
Store in a refrigerator (2-8°C). Keep the vial in the outer carton to protect from light
For storage of diluted product, see enclosed leaflet
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
CV31 3RW UK
Q62247

Module 5

Scientific Discussion During Initial Procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a Marketing Authorisation for Levofolinic Acid 10 mg/ml Solution for Injection, to Mayne Pharma Plc, for use in combination with 5-fluorouracil in cytotoxic therapy or to diminish the toxicity of folic acid antagonists.

This application is made under Article 10.1 of 2001/83 EC, as amended, claiming that Levofolinic Acid 10 mg/ml Solution for Injection is a generic product of Isovorin Solution for Injection (Wyeth Pharmaceuticals). The European reference product is Lederfolin 25mg/2.5ml Solution for Injection (Wyeth-Lederle SpA, Italy) which was granted a licence over 10 years ago.

Levofolinate does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilising folates as a source of "one carbon" moieties. Administration of levofolinate can "rescue" normal cells and thereby prevent toxicity of folic acid antagonists such as methotrexate which act by inhibiting dihydrofolate reductase. Levofolinate can enhance the therapeutic and toxic effects of fluoropyrimidones used in cancer therapy such as 5-fluorouracil.

No new preclinical studies were conducted, which is acceptable given that the application was based on a reference product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on a reference product that has been licensed for over 10 years.

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II ABOUT THE PRODUCT

Name of the product in the Reference Member State	Levofolinic Acid 10 mg/ml Solution for Injection
Name(s) of the active substance(s) (INN)	Calcium levofolinate
Pharmacotherapeutic classification (ATC code)	Detoxifying agents for antineoplastic treatment (V03AF03)
Pharmaceutical form and strength(s)	Solution for injection 10mg/ml
Reference numbers for the Decentralised Procedure	UK/H/0926/001
Reference Member State	United Kingdom
Concerned Member States	Luxemburg, Spain, Belgium and France
Marketing Authorisation Number(s)	PL 04515/0210
Name and address of the authorisation holder	Mayne Pharma Plc Queensway Royal Leamington Spa Warwickshire CV31 3RW UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to calcium levofolinate pentahydrate are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for the drug substance are adequately drawn up. The proposed specification from the active substance manufacturer is in line with the European Pharmacopeia monograph for calcium levofolinate pentahydrate, with additional in-house tests.

Appropriate stability data have been provided to support a retest period of 1 year when stored in the proposed packaging at 2-8°C, protected from light.

All points relating to the restricted part of the Drug Master File have been resolved satisfactorily.

Drug Product
The development of the product has been described; the choice of excipients is justified and their functions are explained. The manufacturing process is described adequately and media fill trials have been performed.

The product specifications cover appropriate parameters for this dosage form. Validation data for the analytical methods have been presented. Batch analysis data have been provided and the results show that the finished product meets the specifications proposed.

The stability data provided support a shelf-life of 18 months, with storage conditions “Store at 2°C – 8°C (in a refrigerator). Store in original container to protect from light.”

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of calcium levofolinate are well known. As calcium levofolinate is a well known active substance, the applicant has not provided additional studies and further studies are not required. Therefore, an overview based on literature review is appropriate.

The non-clinical overview has been written by an independent medical writer who has no formal training in toxicology but has relevant graduate and post-graduate scientific degrees as well as experience in scientific research and medical writing. The report refers to 38 publications prior to the year 2003. The non-clinical overview is adequate.

Section 5.3 of the SPC is acceptable.

Conclusions
There are no objections to the approval of Levofolinic Acid 10 mg/ml Solution for Injection from the non-clinical point of view.

III.3 CLINICAL ASPECTS

Pharmacokinetics
After rapid intravenous administration, serum total tetrahydrofolate (total-THF) concentrations reach a mean peak of 1722 ng/ml. Serum levo-5-methyl-THF concentrations reach a mean peak of 275 ng/ml and the mean time to peak concentration was 0.9 hours. The mean half-life for total-THF and levo-5-methyl-THF is 5.1 and 6.8 hours respectively.

The distribution and plasma levels of levofolinate following intramuscular administration have not been established.

The distribution in tissue and body fluids and protein binding has not been determined. In vivo, levofolinate is converted to levo-5-methyltetrahydrofolic acid (levo-5-methyl-THF), the primary circulating form of active reduced folate. Levofolinate and levo-5-methyl-THF are polyglutamated intracellularly by the enzyme folylpolyglutamate synthetase. Folylpolyglutamates are active and participate in biochemical pathways that require reduced folate.

Levofolinate and levo-5-methyl-THF are excreted renally.

Due to the inherent lack of levofolinate toxicity, the influence of impaired renal or hepatic function on levofolinate disposition was not evaluated.

The applicant’s product contains the same active substance and is of the same concentration as the reference product (Lederfolin 25mg/2.5ml Solution for Injection). It is intended for the same dose regimen and routes of administration (intravenous and intramuscular) and therefore a bioequivalence study is not required. This is in line with current guidelines (Note for guidance on the investigation of bioavailability and bioequivalence, CPMP/EWP/QWP/1401/98).

Pharmacodynamics
Levofolinate does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilising folates as a source of "one carbon" moieties. Levofolinate is actively and passively transported across cell membranes.

Administration of levofolinate can "rescue" normal cells and thereby prevent toxicity of folic acid antagonists, such as methotrexate, which act by inhibiting dihydrofolate reductase.

Levofolinate can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy such as 5-fluorouracil. 5-fluorouracil is metabolised to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FDUMP), which binds to and inhibits thymidylate synthase. Levofolinate is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilise the binding of FDUMP to thymidylate synthase and thereby enhances the inhibition of this enzyme.

Clinical efficacy
No new efficacy data have been submitted for this application and none are required.

Clinical safety
No new safety data have been submitted for this application and none are required.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The important quality characteristics of Levofolinic Acid 10 mg/ml Solution for Injection 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.

An adequate summary of published preclinical data was submitted for this application.

No new or unexpected safety concerns arose from this application.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Bioequivalence study reports were not required. Extensive clinical experience with calcium levofolinate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

Steps Taken After Initial Procedure - Summary

Date submitted	Application type	Scope	Outcome