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FOLOTYN® SOLUTION FOR INFUSION

Mundipharma Middle East FZ LLC

Folotyn is licensed in Lebanon and in Kuwait and awaiting registration in the rest of the Middle East.

Composition

Active substance: pralatrexate.

Excipients: Sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

Pharmaceutical form and quantity of active substance per unit

1 vial with 1 ml solution for infusion contains 20 mg pralatrexate.

Indications/Uses

Treatment of adult patients with peripheral T-cell lymphoma and disease progression after at least one prior treatment. The indication is based on the response rate. No benefit in terms of progression-free survival or overall survival has been demonstrated.

Dosage/Administration

Treatment should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy.

The recommended dose of pralatrexate is 30 mg/m^2, administered as an intravenous infusion over 3-5 minutes, once weekly over a period of 6 weeks, followed by a 1 week rest period and repetition of the 7-week cycle until disease progression or unacceptable toxicity occurs.

Pre-treatment regimen

1 mg vitamin B_{12} i.m. no more than 10 weeks prior to treatment and 1 mg folic acid daily for 10 days before the start of treatment. As of the second dose, the i.m. vitamin B_{12} can be injected with the pralatrexate (every 8-10 weeks). Oral treatment with folic acid at a dose of 1 mg per day should be continued during the full course of therapy, including during the treatment-free interval.

Blood test results

The absolute neutrophil count (ANC) should be ≥1,000/µl and platelet count should be ≥100,000/µl for the first dose and ≥50,000/µl for all subsequent doses. Full blood cell counts should be monitored weekly for all patients receiving pralatrexate. Serum chemistry tests, including renal and hepatic function, should be performed prior to the start of the first and fourth dose of a given cycle, or more often if required.

The dose should be omitted in the event of thrombocytopenia of <50,000/µl or neutropenia of 500-1000/µl that persists for 1 week; if it persists for 2 weeks, treatment should be continued at a reduced dose of 20 mg/m^2. The dose should also be reduced to 20 mg/m2 in the event of the once-only recurrence of thrombocytopenia or neutropenia or in the event of neutropenic fever, and the use of G-CSF or GM-CSF is recommended. Treatment should be discontinued if myelosuppression persists for 3 weeks.

Mucositis

Prior to initiating pralatrexate treatment, mucositis should not exceed Grade 1. Severity of mucositis should be monitored weekly for all patients receiving pralatrexate. In the event of Grade 2 mucositis, the dose should be omitted, and the existing dose can be continued if it improves to Grade ≤1. However, if Grade 2 mucositis returns or Grade 3 mucositis occurs, the dose should be reduced to 20 mg/m^2. Treatment should be discontinued if Grade 4 occurs.

Other treatment-related toxicities

In the event of treatment-related Grade 3 toxicity, the dose should be omitted and continued at 20 mg/m^2 upon recovery to ≤ Grade 2. Treatment should be discontinued in the event of Grade 4 toxicity.

Special dosage instructions

Renal and hepatic impairment

A third of the dose is excreted via the kidneys. Since no studies have investigated patients with renal or hepatic impairment, no recommended dosage can be given.

Elderly patients

No dose adjustment is required in elderly patients with normal renal function.

Paediatric population
The safety and efficacy of Folotyn in paediatric patients have not been investigated. Patients under 18 years of age should not be treated with Folotyn.

Contraindications
Hypersensitivity to the active substance, pregnancy or lactation, treatment with probenecid.

Warnings and precautions
The pretreatment regimen of folic acid and vitamin B_{12} must be strictly observed. The risk of myelosuppression and mucositis is elevated without this treatment. The folic acid dosage may not be increased because this could impair the effect of the pralatrexate. Patients should be asked at regular intervals about their compliance. If they have failed to comply with instructions, treatment should be stopped. The absolute neutrophil count (ANC) should be ≥1,000/µl, the platelet count should be ≥100,000/µl for the first dose and ≥50,000/µl for all subsequent doses. Full blood cell counts should be monitored weekly for all patients receiving pralatrexate. Serum chemistry tests, including renal and hepatic function, should be performed prior to the first and fourth dose of a given cycle, or more often if required. Likewise, the mouth should be examined thoroughly before the start of each dose of pralatrexate. Good oral hygiene (regular mouthwashes, dental hygiene) should be maintained throughout treatment with pralatrexate.

If bone marrow suppression or mucositis occurs during treatment with pralatrexate, the dose should be adjusted in line with the platelet and neutrophil counts, fever and mucositis (see "Posology and method of administration").

Regular inspection of the skin, and particularly areas affected by lymphoma, is essential during treatment.

Serious and potentially life-threatening events, including exfoliative dermatitis, skin necrosis and toxic epidermal necrolysis (involving a fatal outcome in some cases) have been observed. Most at risk are patients with extensive skin involvement or a history of adverse skin reactions. The first signs usually appear at an early stage of treatment. The reactions may increase in severity with further treatment. Treatment must be discontinued if severe dermatological reactions (Grade 4) occur.

Caution should be used in the concomitant administration of substances that are subject to renal tubular secretion (e.g. NSAIDs, penicillins, omeprazole or pantoprazole), since these my result in reduced clearance of pralatrexate.

Nephrotoxic medicinal products (e.g. aminoglycosides, loop diuretics, platinum compounds, cyclosporine) should be avoided.

Etoposide, teniposide and methotrexate should not be administered concurrently with pralatrexate because these substances reduce the clearance of pralatrexate.

Trimethoprim/sulfamethoxazole has been reported in rare cases to increase bone marrow suppression in patients treated with methotrexate, presumably because of the increased antifolate effect. Caution is therefore advised during the concomitant use of these medicinal products with pralatrexate.

Men and women of childbearing age must use an effective method of contraception during treatment with pralatrexate. Pralatrexate may have genetically damaging effects. Male patients are advised not to father a child during treatment and for up to 6 months thereafter. A barrier method or abstinence are recommended.

There are no human data on the effect of pralatrexate on fertility. No fertility studies have been performed in animals. Due to the potential of antifolates to irreversibly affect fertility, patients should be offered appropriate counselling.

Interactions
No formal interaction studies have been performed.

In vitro studies indicate that pralatrexate is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP450) isoenzymes and thus has low potential for drug-drug interactions during metabolism by CYP450 isoenzymes (see "Pharmacokinetics").

The co-administration of increasing doses of probenecid resulted in reduced clearance of pralatrexate (see "Contraindications").

Pralatrexate did not significantly inhibit P-glycoprotein (P-gp), breast cancer resistant pro-

tein (BCRP), organic cation transporter 2 (OCT2), or organic anion transporters 1, 3 and P1B3 (OAT1, OAT3 and OATP1B3). Pralatrexate was a weak inhibitor of organic anion transporter P1B1 (OATP1B1, 35% inhibition at 100 µM) and multidrug resistance-associated protein 2 (MRP2; IC50 = 43.5 µM). Since pralatrexate was found to be a potent inhibitor of multidrug resistance-associated protein 3 (MRP3; IC50 <0.3 µM), a liver transporter implicated in transport of etoposide, teniposide, and methotrexate, caution is advised with concomitant use of these agents with pralatrexate.

Pregnancy/Lactation

Pregnancy

There are no data on the use of pralatrexate in pregnant women. Studies in animals have shown reproductive toxicity (see "Preclinical data"). Other antifolates of the same class have caused teratogenic effects in humans. Folotyn should not be used during pregnancy or in women of childbearing age who are not using contraception (see "Contraindications"). If the patient becomes pregnant while receiving pralatrexate, the patient should be informed of the possible risk to the foetus.

Lactation

Folotyn should not be used in breast-feeding mothers (see "Contraindications"), alternatively, breast-feeding should be stopped beforehand.

Effects on ability to drive and use machines

No studies have been performed. Patients should be advised that they may experience fatigue, blurred vision, or dizziness during treatment with Folotyn. Patients should be advised against driving or using machines if they experience any of these adverse reactions.

Undesirable effects

The most frequent adverse reactions were mucositis (68%, Grade 3/4: 22%), thrombocytopenia (40%, Grade 3/4: 31%), nausea (33%, Grade 3/4: 4%), anaemia (32%, Grade 3/4: 16%), fatigue (30%, Grade 3/4: 6%), neutropenia (24%, Grade 3/4: 21%), epistaxis (23%, Grade 3/4: 0%), vomiting (21%, Grade 3/4: 2%) and constipation (21%, Grade 3/4: 0%).

The most serious adverse reactions were bone marrow suppression (thrombocytopenia, neutropenia and anaemia), mucositis, exfoliative dermatitis, toxic epidermal necrolysis and tumour lysis syndrome.

Other common Grade 3/4 adverse reactions were skin ulcers, infections, anorexia, dyspnoea, vomiting, nausea, pains and fatigue.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from available data).

Infections and infestations

Common: Sepsis, pneumonia, bronchitis, urinary tract infection, cellulitis, herpes zoster, abscess, infection, herpes virus infection, upper respiratory infection, fungal infection, folliculitis

Uncommon: Clostridium difficile colitis, cytomegalovirus colitis

Neoplasms

Uncommon: Tumour lysis syndrome

Blood and lymphatic system disorders

Very common: Neutropenia (24%), leukopenia (11%), thrombocytopenia (40%), anaemia (32%)

Common: Febrile neutropenia, pancytopenia, lymphopenia

Uncommon: Haemolytic anaemia

Metabolism and nutrition disorders

Very common: Anorexia (12%)

Common: Hyperkalaemia, hypokalaemia, dehydration, hyperuricaemia, hyperglycaemia, hypomagnesaemia, hypophosphataemia, weight loss

Uncommon: Hypercalcaemia

Psychiatric disorders

Common: Insomnia, anxiety

Nervous system disorders

Common: peripheral neuropathy, headache, dizziness, paraesthesia, hypoaesthesia

Uncommon: Syncope, memory impairment

Eye disorders

Common: blurred vision, eye irritation, increased lacrimation, ocular hyperaemia, eye pruritus

Uncommon: Reduced visual acuity, uveitis, photopsia, eyelid ptosis, conjunctivitis

Ear and labyrinth disorders
Common: Tinnitus
Uncommon: Deafness, vertigo, hypoacusis

Cardiac disorders
Common: Tachycardia
Uncommon: Cardiorespiratory arrest, cardiomegaly, ejection fraction reduced

Vascular disorders
Common: Hypotension
Uncommon: Venous thrombosis

Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis (23%)
Common: Pleural effusion, dyspnoea, cough, pharyngolaryngeal pain, dysphonia
Uncommon: Pneumonitis, pulmonary embolism, hypoxia, pulmonary congestion, pleuritic pain

Gastrointestinal disorders
Very common: Mucositis (68%), vomiting (21%), diarrhoea (17%), nausea (33%), constipation (21%)
Common: Abdominal pain, odynophagia, oral pain, dyspepsia, rectal haemorrhage, dry mouth
Uncommon: Pancreatitis

Hepatobiliary disorders
Very common: elevated liver enzymes (ASAT 17%, ALAT 16%)
Common: Hepatosplenomegaly, hyperbilirubinaemia
Uncommon: Cholangitis

Skin and subcutaneous tissue disorders
Very common: Rash (11%)
Common: Skin ulcers, urticaria, pruritus, skin haemorrhage, periorbital oedema, erythema, alopecia, dry skin
Uncommon: Exfoliative dermatitis, toxic dermatitis, night sweats
Not known: Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Very common: Musculoskeletal pain (11%)
Common: Back pain, neck pain, arthralgia, myalgia, muscle spasms
Uncommon: Costochondritis, joint swelling

Renal and urinary disorders
Common: Elevated blood creatinine
Uncommon: Renal failure

General disorders and administration site conditions
Very common: Pyrexia (19%), peripheral oedema (18%), fatigue (30%)
Common: Influenza-like illness, chest pain, chills, pain, asthenia, facial oedema
Uncommon: Infusion-related reaction

Overdose
No experience of pralatrexate overdosage has been acquired.
No information is available on the treatment of overdose of Folotyn. The prompt administration of folinic acid, adequate hydration and alkalinisation of the urine should be considered.

Properties/Effects
ATC code: L01BA05

Mechanism of action
Pralatrexate is a folate antagonist which accumulates in tumour cells by binding to folate transporter proteins, including Reduced Folate-Carrier 1 (RFC-1), and as a substrate of folylpolyglutamyl synthetase (FPGS), resulting in disruption of DNA synthesis and subsequent tumour cell death via the inhibition of dihydrofolate reductase (DHFR).

Pharmacodynamic effect
In vitro tests with various human lymphoma cells and *in vivo* investigations with human xenograft tumour models showed significant cytotoxicity and a reduction in tumour growth.

Clinical efficacy
In an open-label, uncontrolled, non-randomised study, 115 patients with peripheral T-cell lymphoma that progressed after at least one course of chemotherapy were treated with Folotyn 30 mg/m^2 until the onset of disease progression or unacceptable toxicity. Of the 111 patients treated, 109 patients were evaluable for efficacy.
The average age was 54 years and the median number of prior therapies was three (1-12).

The primary efficacy endpoint was the overall response rate (complete response (CR), complete response unconfirmed (CRu) and partial response (PR)), as assessed in an independent central review using the International Workshop Criteria (IWC). This was 29% (CR+CRu 11%, PR 18%). The median duration of response was 10.1 months.

Approximately two-thirds of patients (63%, n = 69) did not have evidence of response to their most recent prior therapy before entering the study. Of these 69 patients, 25% responded to pralatrexate. Approximately a quarter of the patients (24%, n = 26) had not responded to any of the previous therapies. Of these 26 patients, 19% responded to pralatrexate.

Pharmacokinetics

Pralatrexate is a 1:1 racemic mixture of R- and S-diastereomers at the C10 chiral centre.

Absorption

The mean C_{max} value for pralatrexate in PTCL patients is 5.8 µg/ml and the mean total systemic exposure ($AUC_{(0-\infty)}$) is 268 µg/ml·min.

Distribution

In the pivotal study with PTCL patients, pralatrexate diastereomers showed steady-state volumes of distribution of 105 l (S-diastereomer) and 37 l (R-diastereomer) respectively.

The protein binding of pralatrexate is low (67%-86%).

Metabolism

Pralatrexate is not significantly metabolised by CYP450 isoenzymes or glucuronidases.

Elimination

The total systemic clearance of pralatrexate diastereomers is 417 ml/min. (S-diastereomer) and 191 ml/min. (R-diastereomer). The terminal elimination half-life of pralatrexate is 12-18 hours (coefficient of variance (CV) = 62-120%). 31% of the S-diastereomer and 38% of the *R diastereomer* are excreted in urine. Elimination via the faeces has not been recorded.

Kinetics in specific patient groups

No investigations have been performed.

Preclinical data

Pralatrexate was not mutagenic in standard *in vitro* and *in vivo* mutagenicity assays (Ames test, chromosome aberration assay in Chinese hamster ovary (CHO) cells and mouse micronucleus assay). However, these tests may not reliably predict genotoxicity for this class of compounds. Based on experience with other antifolates, an increased risk for genotoxicity from pralatrexate treatment cannot be excluded.

Carcinogenicity studies have not been performed with pralatrexate.

No fertility studies have been performed. In rats and rabbits, pralatrexate was embryotoxic and foetotoxic at intravenous doses. In rats, pralatrexate caused a dose-dependent decrease in foetal viability, manifested as an increase in late, early and total resorptions. There was also a dose dependent increase in post implantation loss. In rabbits, the observed toxicity manifested itself as early and total resorptions, post implantation loss and a decrease in the total number of live foetuses.

Further information

Folotyn is administered undiluted as an intravenous infusion over 3-5 minutes. The calculated dose should be aseptically withdrawn into a syringe and administered via the side port of a free flowing sodium chloride 9 mg/ml (0.9%) solution for injection intravenous line. Folotyn must not be administered by any other route of administration.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

This medicinal product must not be used after the expiry date (“EXP”) printed on the container.

The ready-to-use Folotyn solution for infusion contains no preservatives and is intended for single use only. After withdrawal of dose, discard any unused portion left in the vial. Unused portions should not be saved for later administration.

Special precautions for storage

Store in the refrigerator (2-8°C) out of the reach of children.

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

Unopened vials may be removed from the refrigerator and stored at up to 30°C for a single period of up to 120 hours.

Instructions for handling

The rules for cytotoxic agents should be observed when preparing and handling Folotyn.

Folotyn is a clear, yellow solution.

The vials should be inspected visually for particulate matter and discolouration prior to administration. Vials exhibiting particulate matter or discolouration should not be used.

Packs

1 vial of 20 mg/1 ml solution for infusion [A]

Marketing authorisation holder

Mundipharma Medical Company, Hamilton/ Bermuda, Basel Branch (I.A.C of Mundipharma)
St. Alban-Rheinweg 74, CH-4020 Basel, Switzerland

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