Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Pemetrexed 10 mg/ml solution for infusion

pemetrexed disodium hemipentahydrate

PL 17780/1156

Zentiva Pharma UK Limited

LAY SUMMARY

Pemetrexed 10 mg/ml solution for infusion
pemetrexed disodium hemipentahydrate

This is a summary of the Public Assessment Report (PAR) for Pemetrexed 10 mg/ml solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Pemetrexed in this lay summary for ease of reading.

For practical information about using Pemetrexed, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Pemetrexed and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the United Kingdom (UK) called Alimta 500 mg powder for concentrate for solution for infusion, albeit with certain differences. In this case, the differences between Pemetrexed solution for infusion compared to the reference product are a change in pharmaceutical form and a change in strength.

This product has been authorised by MHRA for the United Kingdom. This procedure takes into account the outcome of a decentralised (DC) procedure in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 24 November 2021 (DE/H/6705/001/DC). This is known as the MR/DC Reliance Procedure.

Pemetrexed is a medicine used in the treatment of cancer. Pemetrexed is given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma, a form of cancer that affects the lining of the lung, to patients who have not received prior chemotherapy.

Pemetrexed is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

Pemetrexed can be prescribed in patients who have lung cancer at an advanced stage, in cases where the disease has responded to treatment or if the cancer remains largely unchanged after initial chemotherapy. In advanced stage of lung cancer, Pemetrexed is also a treatment for patients whose disease has progressed after other initial chemotherapy has been used.

How does Pemetrexed work?
Pemetrexed interferes with the production of certain building blocks of DNA in cancer cells.

How is Pemetrexed used?
The pharmaceutical form of this medicine is a solution for infusion and the route of administration is infusion into a vein (intravenous).

This medication is a ‘Ready to use solution’ for Infusion and should not be further diluted. This can lead to significant under-dosing in the patient. No reconstitution is required before administration.

The dose of Pemetrexed is 500 milligrams for every square metre of the surface area of the patient's body. The patient's height and weight are measured to work out the surface area of the body. The doctor will use this body surface area to work out the right dose for their patient. The dose may be adjusted, or treatment may be delayed depending on the patient's blood cell counts and on the general condition of their patient.

Pemetrexed will always be delivered by infusion into one of the veins. The infusion will last approximately 10 minutes.

For further information on how Pemetrexed is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Pemetrexed have been shown in studies?
No additional studies were needed as Pemetrexed contains the same active substance as the reference medicine, and satisfactory data to justify the differences have been provided.

What are the possible side effects of Pemetrexed?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk/ or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Pemetrexed (which may affect more than 1 in 10 people) are:

- Infection
- Pharyngitis (a sore throat)
- Low number of neutrophil granulocytes (a type of white blood cell)
- Low white blood cells
- Low haemoglobin level
- Pain, redness, swelling or sores in your mouth
- Loss of appetite
- Vomiting
- Diarrhoea
- Nausea
- Skin rash
- Flaking skin
- Abnormal blood tests showing reduced functionality of kidneys
- Fatigue (tiredness).

Why was Pemetrexed approved?
MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

What measures are being taken to ensure the safe and effective use of Pemetrexed?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Pemetrexed. The RMP details the important risks of Pemetrexed, how these risks can be minimised, any uncertainties about Pemetrexed (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Pemetrexed:
Important identified risks:

- Non-compliance with folic acid and Vitamin 812 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities
- Bone marrow suppression
- Gastrointestinal disorders
- Renal disorders
- Sepsis
- Bullous skin reaction including SJS and TEN
- Interstitial pneumonitis
- Radiation pneumonitis
- Radiation recall

Important potential risks: None
Missing information: None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Pemetrexed are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Pemetrexed
A marketing authorisation was granted in the United Kingdom on 13 May 2022.

The full PAR for Pemetrexed follows this summary.

This summary was last updated in June 2022.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Pemetrexed 10 mg/ml solution for infusion (PL 17780/1156) could be approved.

The product is approved for the following indications:
Malignant pleural mesothelioma
Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer
Pemetrexed in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

Pemetrexed is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

This product has been authorised by MHRA for the United Kingdom. This procedure takes into account the outcome of a decentralised (DC) procedure in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 24 November 2021 (DE/H/6705/001/DC). This is known as the MR/DC Reliance Procedure.

For the scientific discussion of the quality, non-clinical and clinical assessment conducted during the DC procedure, please refer to the Reference Member State (RMS) Public Assessment Report, available on the RMS regulatory agency website or on the Heads of Medicines Agencies website.

This application was approved under Regulation 52B of the Human Medicines Regulation 2012, as amended (previously Article 10.3 of Directive 2001/83/EC, as amended).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing Authorisation was granted on 13 May 2022.

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation is recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation is recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Pemetrexed Koanaa 10 mg/ml concentrate for solution for infusion' (100 mg & 500 mg powder for concentrate for solution for infusion). The bridging report submitted is acceptable, and is also supported by the similarities between the PIL of Alimta 500 mg powder for concentrate for solution for infusion and this product.

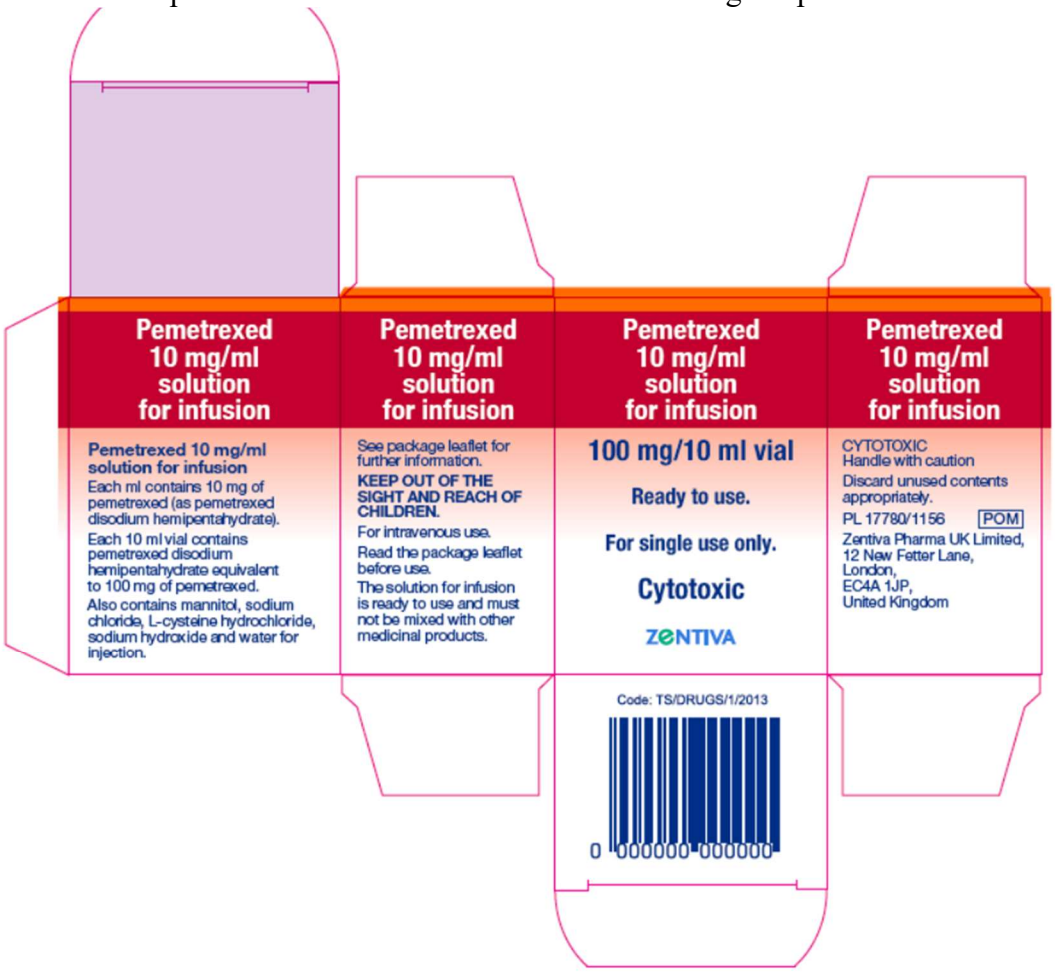
VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

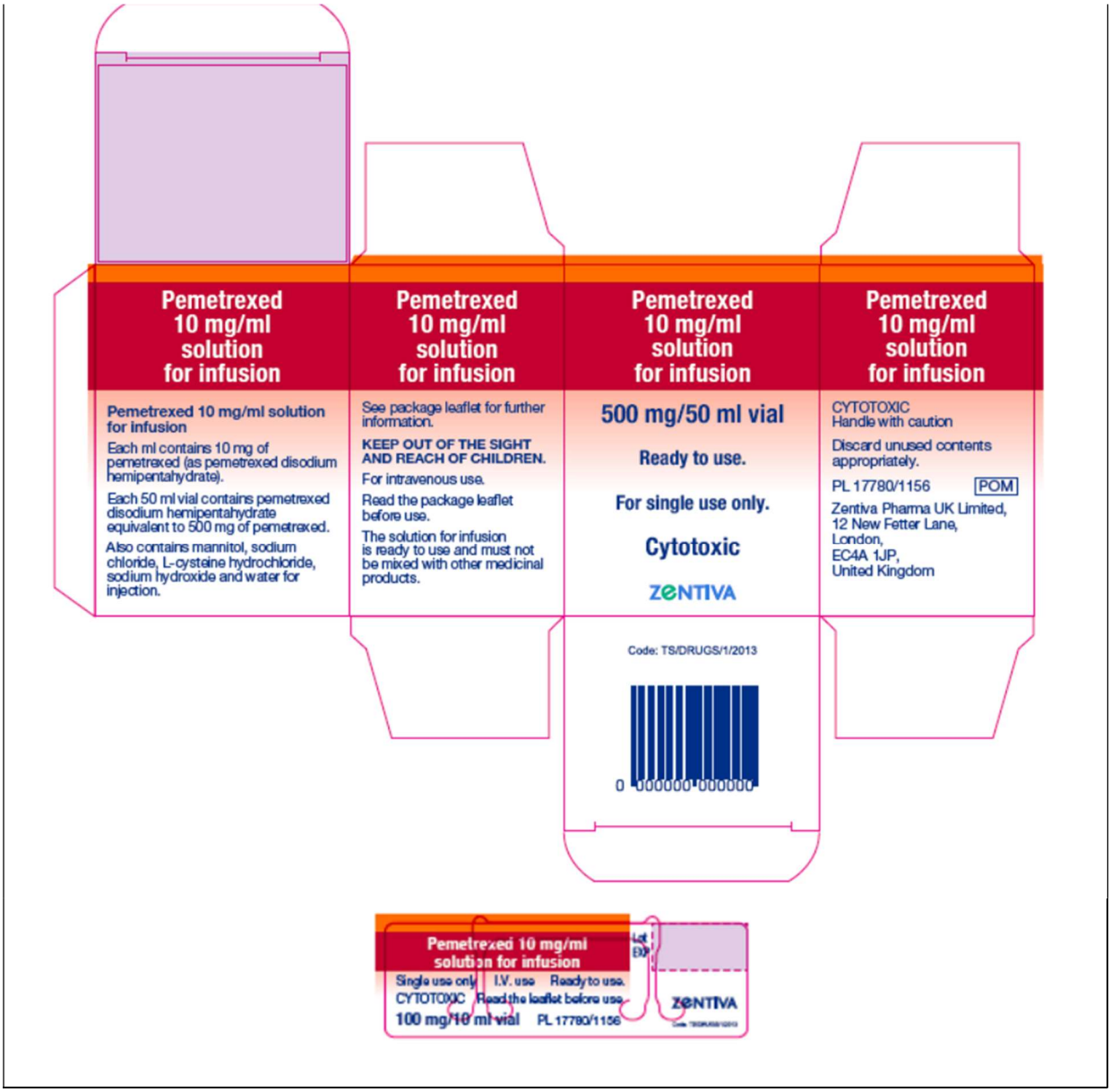
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.




Pemetrexed 10 mg/ml solution for infusion
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Pemetrexed 10 mg/ml solution for infusion
Pemetrexed 10 mg/ml solution for infusion
Each ml contains 10 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
Each 50 ml vial contains pemetrexed disodium hemipentahydrate equivalent to 500 mg of pemetrexed.
Also contains mannitol, sodium chloride, L-cysteine hydrochloride, sodium hydroxide and water for injection.
See package leaflet for further information.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
For intravenous use.
Read the package leaflet before use.
The solution for infusion is ready to use and must not be mixed with other medicinal products.
500 mg/50 ml vial
Ready to use.
For single use only.
Cytotoxic
ZENTIVA
CYTOTOXIC
Handle with caution
Discard unused contents appropriately.
PL 17780/1156
POM
Zentiva Pharma UK Limited,
12 New Fetter Lane,
London,
EC4A 1JP,
United Kingdom
Code: TS/DRUGS/1/2013
0
Pemetrexed 10 mg/ml solution for infusion
Single use only
I.V. use
Ready to use.
CYTOTOXIC
Read the leaflet before use.
100 mg/10 ml vial
PL 17780/1156
ZENTIVA

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**