21 July 2016
EMA/CHMP/485042/2016
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Pemetrexed ditromethamine Hospira

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/004306/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

API	Active pharmaceutical ingredient
ASMF	Active Substance Master File
BSA	Body Surface Area
DMF	Drug master File
LoD	Limit of Detection
LoQ	Limit of Quantification
MAA	Marketing authorisation application
NfG	Note for Guidance
Ph. Eur.	European pharmacopoeia
RMP	Risk Management Plan

1. Recommendation

Based on the CHMP review of the data on quality, safety, clinical and risk management plan, the CHMP considers that the generic application for Pemetrexed (as Ditromethamine) Hospira in the treatment of

Malignant pleural mesothelioma

Pemetrexed (as Ditromethamine) Hospira in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed (as Ditromethamine) Hospira 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 (as Ditromethamine) Hospira 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 (as Ditromethamine) Hospira 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.

could be approvable provided that satisfactory answers are given to the "other concerns".

Questions to be posed to additional experts

Inspection issues

GMP inspection(s)

The EMA Compliance and Inspection Service has reviewed the manufacturer information contained in the application form (Module 1) and available from the EEA National Competent Authorities and determined that all relevant sites have valid manufacturing authorisations or valid GMP certificates as appropriate. Hence, no GMP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

GCP inspection(s)

N/A

2. Executive summary

2.1. Problem statement

N/A

2.2. About the product

This centralised application concerns a generic version of pemetrexed (as ditromethamine) powder for concentrate for solution for infusion. Pemetrexed (as Ditromethamine) Hospira powder for concentrate for solution for infusion 100 mg, 500 mg or 1000 mg per vial (25 mg/ml) has been developed as a pharmaceutical equivalent of ALIMTA (Eli Lilly).After reconstitution, each vial contains 25 mg/ml of pemetrexed.

The applied indication of Pemetrexed (as Ditromethamine) Hospira is

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 (see section 5.1).

As monotherapy or in combination with cisplatin the recommended dose of pemetrexed is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

The recommended dose of cisplatin is 75 mg/m^2 BSA infused over 2 hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle.

Main safety concerns are haematological, gastrointestinal toxicities and skin reactions.

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. To reduce haematological toxicity, patients treated with pemetrexed must also receive folic acid and vitamin B12 supplementation.

Patients should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving treatment.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

In May 2015 the Applicant Hospira UK Limited requested scientific advice for their product Pemetrexed (as Ditromethamine) Hospira pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council (procedure No: EMEA/H/SA/3144/1/2015/III).

2.4. General comments on compliance with GMP, GLP, GCP

No issues have been identified that specifically demand for an inspection.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application has been submitted in accordance with Regulation 726/2004, a generic of a centrally authorised product. An application has been submitted in accordance with the Article 10(1) a generic application in directive 2001/83/EC.

3. Scientific overview and discussion

Pemetrexed was first authorised in EU on 2004 via centralised procedure – innovator product Alimta.

Pemetrexed is an antifolate antimetabolite which inhibits multiple enzymes involved in folate metabolism, and pyrimidine and purine synthesis. Inhibition of these enzymes results in impeded synthesis of nucleotides and in turn leads to inhibition of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis.

Pemetrexed has multiple intracellular loci within the folate pathway. By competing with reduced folate for binding sites, pemetrexed disrupts the activity of multiple folate-requiring enzymes including thymidylate synthase (TS), dihydrofolatereductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT) and aminoimidazole carboxamide formyltransferase (AICARFT).

Pemetrexed has a pyrrole ring that replaces the pyrazine ring in the pterine portion of folic acid and a methylene group that replaces the benzylic nitrogen in the bridge portion of folic acid.

Pemetrexed is indicated for malignant pleural mesothelioma (in combination with cisplatin) and for non-small cell lung cancer (in combination with cisplatin or as monotherapy).

Main safety concerns are haematological, gastrointestinal toxicities and skin reactions.

To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. To reduce haematological toxicity, patients treated with pemetrexed must also receive folic acid and vitamin B12 supplementation.

Patients should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving treatment.

3.1. Quality aspects

3.1.1. Introduction

The active substance pemetrexed is a member of the antifolate antimetabolite therapeutic class. Pemetrexed is chemically similar to folic acid and the antitumour activity is likely derived from inhibition of several key folate-requiring enzymes, leading to depletion of fully reduced folate, and ultimately resulting in disruption of nucleotide synthesis for both pyrimidines and purines.

The active substance is Pemetrexed ditromethamine. It is not described in the European Pharmacopoeia, pharmacopoeias of the member states or USP. However Pemetrexed disodium heptahydrate has a valid Ph. Eur. monograph since April 2013.

The documentation is presented as an Active Substance Master File. Additional data have also been presented from the drug product manufacturer.

3.1.2. Active Substance

General Information

General properties of the substance have been properly described. Pemetrexed has pH dependent solubility in water.

Manufacture, characterisation and process controls

The active substance Pemetrexed ditromethamine is manufactured by one manufacturer. The API is sufficiently characterised, it is defined as Pemetrexed ditromethamine dihydrate form. The possible impurity profile of drug substance has been discussed in detail.

Specification

The active substance specification is in line with the General Monograph “Substances for pharmaceutical use” 04/2013:2034 and ICH Q3A and Q6A guidelines. In general the quality control as applied by the finished product manufacturing site is considered adequate, still the applicant has to justify the wider limits for water content or the quality requirements should be tightened accordingly. The limit for potential catalyst content should also be included in the specifications, the corrected specifications are requested.

The methods used are described in detail. The validation data provided are in accordance with the requirements of the relevant ICH guidelines. Sufficient information for the reference standards has been provided.

Stability

Pemetrexed ditromethamine is stored in tightly closed containers, protected from light. The container closure system consists of polyethylene bags (primary) and HDPE drums (secondary). The stability program is carried out according to ICH guidelines on stability testing. Results of three production batches were presented over a period up to 18 months at long-term conditions and six months at accelerated conditions. All data are within specifications and no significant changes are observed. The proposed storage condition need to be confirmed otherwise the data as submitted in the ASMF are not considered sufficient and no re-test period should be applied.

Comparability exercise for Active Substance

Not applicable

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Pemetrexed (as Ditromethamine) Hospira 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion is a sterile lyophilized plug, which is intended to be reconstituted and then diluted with a suitable intravenous solution prior to administration. The packaging components are Type 1 10/50/100 mL clear glass vial, 20 mm bromobutyl rubber closure and 20 mm aluminium seal with flip-off top.

A different salt form of the active substance (pemetrexed ditromethamine) has been selected for the Hospira product compared to the reference product Alimta marketed by Eli Lilly (pemetrexed disodium). The excipients are comparable with the reference product however no pH adjusting agents have been used within the composition. All proposed presentations (100/500/1000 mg/vial) are qualitatively and quantitatively proportional. The route of administration, dosage form, and concentration (25 mg/ml) of Pemetrexed for Injection after reconstitution is the same as that of the reference product. Subsequently, Hospira has also developed an additional 1 g/vial presentation to facilitate administration of Pemetrexed for Injection in patients exceeding a body surface area (BSA) of 1 m^2. All ingredients were formulated to match the reference product for each specific attribute. No alternative formulations were investigated.

Manufacture of the product and process controls

The manufacturing process involves solution preparation/compounding, pre-filtration, final filtration, filling and lyophilisation. All manufacturing processes are routinely used in parenteral drug product manufacturing. The drug product is manufactured by aseptic processes. Terminal sterilisation was not appropriate for the formulation as it affected the quality of the drug product thus sterilisation by filtration (through bacterial retentive filter) followed by aseptic processing was developed as suitable method of sterilisation for the product. Process validation for the registration batches of Pemetrexed ditromethamine 100 mg/vial, 500 mg/vial and 1g/vial are considered acceptable. The applicant commits to conduct prospective process validation of the first three (consecutive) production-scale batches accordingly. However, aseptic filling is considered a non-standard process and per Annex II to Note for Guidance on Process Validation (CPMP/QWP/2054/03), results of the drug product manufacturing process´ validation in industrial batches should be submitted within initial application. Hence the maximum proposed batch sizes are not accepted until the validation data presented accordingly.

Product specification

Specifications conform to compendial general chapters where relevant and ICH requirements. Set acceptance criteria are considered generally adequate however according to the obtained results shelf-life limit for assay should be tightened. The applicant should also tighten the release and shelf-life limits for “total impurities”.

Stability of the product

The applicant proposes a shelf-life of 18 months when stored below 25°C. The 6 months stability study results are available at the moment. Test results for all strengths at long term, intermediate and accelerated conditions were in accordance with the applied acceptance criteria. The extrapolated shelf-life may be up to twice beyond the period covered by real time data (CPMP/QWP/122/02, rev 1 corr). Hence the shelf-life can be extended to 12 months based on the presented data. Onward extension is possible when further stability data are available. As the stability study results remain within specifications also at accelerated conditions, the restrictions are not appropriate and should be amended to “This medicinal product does not require any special storage conditions”. According to the reconstitution study the drug product is stable for up to 24 hours after reconstitution when stored at 5°C ± 3°C, protected from light. The comparative infusion stability study compared the stability of the drug product with the reference product under the same conditions (24 hours at 5±3°C in the absence of light, both in PVC and polyolefin bags). To support the applicant`s proposal for the shelf-life, further stability results and updated comparative infusion stability study should be presented as according to

the Note for Guidance on In-use Stability Testing of Human medicinal Products (CPMP/QWP/2934/99) and one of the batches should be chosen towards the end of its shelf life.

Comparability exercise for Finished Medicinal Drug Product

N/A

Adventitious agents

N/A

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

Several questions have been raised with respect to the quality the drug product. The detailed information is given in the quality part of the assessment report.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

It can be concluded that before Pemetrexed ditromethamine 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion could be recommended for approval, satisfactory responses to the other concerns should be provided.

3.2. Non clinical aspects

No new data were presented. This is acceptable.

3.2.1. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed (as Ditromethamine) Hospira manufactured by Hospira is considered unlikely to result in any significant increase in the combined sales volumes for all pemetrexed containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

3.2.2. Conclusion on non-clinical aspects

There are no objections to approval of Pemetrexed (as Ditromethamine) Hospira from a non-clinical point of view.

3.3. Clinical aspects

3.3.1. Pharmacokinetics

The product is to be administered as an intravenous infusion containing pemetrexed ditromethamine instead of pemetrexed sodium. Pemetrexed (as ditromethamine) for Injection (100mg/vial; 500mg/vial; 1000mg/vial) contains the same active substance as the reference product Pemetrexed sodium (ALIMTA). Pemetrexed (as ditromethamine) for Injection is conjugated to a tromethamine salt instead of sodium salt. The Applicant demonstrated that in a watery environment, both Pemetrexed (as ditromethamine) for Injection and ALIMTA contain the same amount of pemetrexed as free base. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence.

3.3.2. Pharmacodynamics

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.3.3. Conclusions on clinical aspects

There are no objections to approval of Pemetrexed (as Ditromethamine) Hospira from a clinical point of view.

3.4. Risk management plan

Safety concerns

Table 1: Summary of the Safety Concerns (table from the applicant)

Summary of safety concerns	
Important identified risks	Renal Disorders Non-compliance with folic acid and vitamin B12 regimens, manifested mainly as haematological and gastrointestinal toxicities. Radiation pneumonitis Radiation recall Gastrointestinal disorders Interstitial pneumonitis Sepsis Bullous skin reactions including SJS and TEN Bone marrow suppression
Important potential risks	None
Missing information	None

Having considered the data in the safety specification, the Rapporteur agrees that the safety concerns listed by the Applicant are appropriate.

Pharmacovigilance plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The 1000 mg strength does not exist for the reference product. Therefore, PRAC and CHMP estimate that, even if not listed as a specific risk in the RMP of Pemetrexed Hospira, the risk of medication error should be under specific surveillance by the MAH. Should a significant increase in the frequency of reported medication errors be detected, the MAH should report this as a signal.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2: Proposal from applicant for risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Renal Disorders	**Proposed text in SmPC – Special warnings and precautions in section 4.4**. "Patients receiving Pemetrexed should be monitored before each dose with a blood chemistry tests to evaluate renal and hepatic function". "Serious renal events, including acute renal failure, have been reported with Pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events, including dehydration or pre-existing hypertension or diabetes". Renal Disorders is listed as an ADR in **section 4.8** of the SmPC. **Proposed text in PIL** – Possible side effects in section 4. Uncommon side effect includes acute renal failure.	None Proposed
Non-compliance with folic acid and vitamin B12 regimens, manifested mainly as haematological and gastrointestinal toxicities.	**Proposed text in SmPC - Posology and method of administration in section 4.2**. "To reduce toxicity, patients treated with Pemetrexed must also receive vitamin supplementation. Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of Pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of Pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1,000 micrograms) in the week preceding the first dose of Pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as Pemetrexed". **Proposed text in PIL – How to use Pemetrexed in section 3** "Vitamin B12 and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment".	None Proposed
Radiation pneumonitis	**Proposed text in SmPC – Special warnings and precautions in section 4.4**. "Particular attention should be paid to these patients, and caution exercised with use of other radiosensitising agents". Radiation pneumonitis is listed as an ADR **in section 4.8** of the SmPC. **Proposed text in PIL – Possible side effects in section 4.** "Radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) may occur in patients who are also treated with radiation either before, during or after their Pemetrexed therapy".	None Proposed
Radiation recall	**Proposed text in SmPC – Special warnings and precautions in section 4.4**. "Particular attention should be paid to these patients, and caution	None Proposed

	exercised with use of other radiosensitising agents". Radiation recall is listed as an ADR in **section 4.8** of the SmPC. **Proposed text in PIL – Possible side effects in section 4**. "Radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation".	
Gastrointestinal disorders	**Proposed text in SmPC – Special warnings and precautions in section 4.4**. "Due to the gastrointestinal toxicity of Pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving treatment" "If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity" Gastrointestinal disorders is listed as an ADR **in section 4.8** of the SmPC.	None Proposed
Interstitial pneumonitis	**Proposed text in SmPC – Undesirable effects in section 4.8**. "In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with Pemetrexed" **Proposed text in PIL – Possible side effects in section 4.** Uncommon side effect – "Interstitial pneumonitis (scarring of the air sacs of the lung)".	None Proposed
Sepsis	**Proposed text in SmPC – Undesirable effects in section 4.8**. "Sepsis, sometimes fatal, has been commonly reported during clinical trials with Pemetrexed". "Fever or infection (common): if you have a temperature of 38ºC or greater, sweating or other signs of infection (since you might have fewer white blood cells than normal which is very common). Infection (sepsis) may be severe and could lead to death". **Proposed text in PIL – Possible side effects in section 4**. "Fever or infection (common): if you have a temperature of 38ºC or greater, sweating or other signs of infection (since you might have fewer white blood cells than normal which is very common). Infection (sepsis) may be severe and could lead to death".	None Proposed
Bullous skin reactions including SJS and TEN	**Proposed text in SmPC – Undesirable effects in section 4.8.** "Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal". **Proposed text in PIL- Possible side effects in section 4.** "Allergic reaction: if you develop skin rash (very common) / burning or prickling sensation (common), or fever (common). Rarely, skin reactions may be severe and could lead to death. Contact your doctor if you get a severe rash, or itching, or blistering (Stevens-Johnson syndrome or toxic epidermal necrolysis."	None Proposed
Bone marrow suppression	**Proposed text in SmPC – Undesirable effects in section 4.4**: "Pemetrexed can suppress bone marrow function as	None Proposed

	manifested by neutropenia, thrombocytopenia, and anaemia (or pancytopenia) (see section 4.8)" **Proposed text in SmPC – Undesirable effects in section 4.8**: "The most commonly reported undesirable effects related to Pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leucopenia, thrombocytopenia"	
Important potential risks		
None	Guidance in SPC Section 4.4 "Special warnings and precautions for use"	None Proposed
Missing Information		
None	Guidance in SPC Section Section 4.6 "Fertility, pregnancy and lactation"	None Proposed

In line with the reference product, the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

The CHMP and PRAC considered that the RMP version 5.0 could be acceptable provided an updated RMP and satisfactory responses to the list of questions are submitted.

3.5. Pharmacovigilance system

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance system at this time.

4. Benefit/risk assessment

A benefit/risk ratio comparable to the reference product can be concluded if satisfactory answers are given to the "other concerns" regarding quality and clinical aspects.