CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Fludarabine - PCH 25 mg/ml, concentrate for solution for intravenous infusion or injection Pharmachemie BV, the Netherlands

fludarabine phosphate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow–organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0715/001/DC
Registration number in the Netherlands: RVG 33255

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Pharmacotherapeutic group:	Antimetabolites, Purine analogues
ATC code:	L01BB05
Route of administration:	intravenous
Therapeutic indication:	treatment of B-cell chronic lymphocytic leukaemia in patients with sufficient bone marrow reserves and as first line treatment in patients with advanced disease, Rai stages III/IV (binet stage C), or Rai stages I/II (binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease
Prescription status:	prescription only
Date of authorisation in NL:	28 June 2007
Concerned Member States:	AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Fludarabine - PCH 25 mg/ml, concentrate for solution for intravenous infusion or injection, from Pharmachemie BV.

The product is indicated for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves and as first line treatment in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.

A comprehensive description of the indications and posology is given in the Summary of Product characteristics (SPC).

Fludarabine phosphate (9-ß-D-arabinofuranosyl-2-fluoro-9H-purin-6-amine-5'-mono-phosphate) is a synthetic purine nucleoside in which the ribose sugar is replaced by arabinose and a fluoride is added to the purine base part. Thus, this nucleoside acts as a purine antagonist antimetabolite. Fludarabine - PCH 25 mg/ml is therefore an antineoplastic agent, relatively resistant to deamination by adenosine deaminase.
Fludarabine phosphate is rapidly dephosphorylated to 2F-ara-A, which is taken up by cells and then phosphorylated intracellularly to the active triphosphate form, 2F-ara-ATP. The ascribed action of intracellular phosphorylated fludarabine is the inhibition of DNA synthesis by competing with deoxy-ATP for incorporation into newly formed DNA. Incorporation of fludarabine results in DNA synthesis termination and also DNA replication enzyme inhibition, eventually resulting in apoptosis. 2F-ara-A elimination is largely by renal excretion. 40 to 60% of the administered iv. dose was excreted in the urine.
Since the early nineties the use of fludarabine phosphate has proven to be a useful drug in the treatment of patients with symptomatic, high stage or refractory chronic lymphatic leukemia (CLL) despite the frequently observed adverse effects (gastro-intestinal complaints, myelosuppression & immunosuppression, infection, fever).
In line with the originator product, the proposed indication of Fludarabine - PCH 25 mg/ml is the treatment of patients with B-cell CLL with sufficient bone marrow reserve. Also, in line with the originator product indication, first-line treatment of CLL with Fludarabine - PCH 25 mg/ml is proposed to be restricted to patients with high grade CLL with disease related symptoms or progressive disease.

This application concerns a hybrid application claiming essential similarity with the innovator product Fludara 50 mg, powder for solution for injection or infusion, which has been registered in the Netherlands by Bayer BV since September 1994. In addition, reference is made to Fludara authorisations in the individual member states (reference product). The difference between Fludarabine - PCH 25 mg/ml and the reference product is the change in the pharmaceutical form. Fludara 50 mg is a lyophilised powder, whereas the current product is a solution for injection or infusion.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC (hybrid application).

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. The authorisation based on article 10(3) is therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Fludarabine - PCH 25 mg/ml is a product for parental use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is fludarabine phosphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for residual solvents, bacterial endotoxins and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 industrial scale batches.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 4 years, when stored in the refrigerator (2°C - 8°C) in the original package, i.e. borosilicate amber glass container, inside a polyester-aluminium-polyester-polypropylene bag. The solid drug substance is not sensitive to light.

The excipients used are common in the manufacture of parenteral formulations and are, according to the SPC of the innovator, also present in the reference product. The excipients comply with the relevant Ph.Eur. monographs. For the control of the excipients the Ph.Eur. methods are used. For sodium hydroxide the applicant has included additional specifications for the microbiological quality and bacterial endotoxins. Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Fludarabine - PCH 25 mg/ml is supplied in vials containing 50 mg of fludarabine phosphate as a sterile, preservative-free, solution with a pH of 6.0 – 7.1. The concentration of fludarabine phosphate is 25 mg/ml in each vial. The excipients are mannitol (E421), sodium hydroxide (for pH adjustments), and water for injections (solvent). The colourless 2-ml type I glass vials have a bromobutyl rubber stopper, an aluminium seal and a polypropylene snap-cap.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Fludarabine PCH has a similar composition as Fludara after reconstitution. The innovator is a powder, whereas the test product is a solution. The packaging materials are usual and suitable for the product.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines.

Quality control of the medicinal product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are based on the monograph for parenteral preparations in the Ph.Eur. and in-house specifications. They include tests for appearance, identity, colour, clarity, pH, assay, degradation, particulate matter, particulate contamination, extractable volume, closure integrity, sterility, and bacterial endotoxins. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product has been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the product for 18 months when stored in the refrigerator. The specific storage condition, do not freeze, is included in the SPC and on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is essentially similar to Fludara, which is available on the European market, after reconstitution. No new pre-clinical data have been submitted, and therefore the application has not undergone pre-clinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of fludarabine phosphate released into the environment. It does not contain any component which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Fludarabine phosphate is a well-known active substance with established efficacy and tolerability.

The composition of Fludarabine - PCH 25 mg/ml, concentrate for solution, is considered to be similar to the innovator's product Fludara, 50 mg powder for solution, when ready to be used.

As Fludarabine - PCH 25 mg/ml is a product for parental use, no bioequivalence study is required (NfG CPMP/EWP/QWP 1401/98). Fludarabine - PCH 25 mg/ml is considered essentially similar (after reconstitution) as the reference product Fludara, 50 mg powder, which is already marketed in various European countries. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply for this application.

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Fludara 50 mg marketed by Bayer BV.

Risk Management Plan
Fludarabine phosphate was first approved in 1994 in the Netherlands, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of fludarabine phosphate can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a

pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed Risk Management Plan is not necessary for this product.

Readability test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test of the package leaflet has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fludarabine - PCH 25 mg/ml concentrate for solution for intravenous infusion or injection is essentially similar to Fludara, 50 mg powder for solution for injection or infusion. Fludara 50 mg, is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parental use, no bioequivalence study is deemed necessary. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The Member States, on the basis of the data submitted, have granted a marketing authorisation for Fludarabine - PCH 25 mg/ml.
There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure. The decentralised recognition procedure was finished on 15 March 2007. Fludarabine - PCH 25 mg/ml was authorised in the Netherlands on 28 June 2007.

A European harmonised birth date has been allocated (11 August 1994) and subsequently the first data lock point for fludarabine phosphate is August 2006. The first PSUR is therefore expected in October 2009, after which a PSUR should be submitted every 3 years.

In order to facilitate synchronisation of the PSUR submission schedule as well as harmonisation of renewal dates, the date for the first renewal is agreed to be April 2010.

The following post-approval commitments were made during the procedure:

Quality- drug product
- The MAH committed to provide validation data of full-scale batch size.
- The MAH committed to perform process validations if greater batch sizes will be employed being part of a future variation procedure.
- The MAH committed to provide in-use stability data at the end of shelf-life.
- The MAH committed to submit results of the continued stability studies, at least up to the proposed storage period.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RH	Relative Humidity
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
The shelf life of the finished product as packaged for sale, changed from 18 months to 30 months.	NL/H/0715/ 001/IB/001	IB	12-7-2007	26-9-2007	Approved	N
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material /reagent/intermediate of the active substance; from a manufacturer currently approved.	NL/H/0715/ 001/IA/002	IA	19-10-2007	2-11-2007	Approved	N
Change in the re-test period of the active substance.	NL/H/0715/ 001/IB/003	IB	19-10-2007	19-11-2007	Approved	N
Change in the shape or dimensions of the container or closure. Sterile pharmaceutical forms and biological medicinal products.	NL/H/0715/ 001/IB/004	IB	17-10-2007	19-11-2007	Approved	N
Change in the name and/or address of the marketing authorisation.	NL/H/0715/ 001/IA/005	IA	10-10-2007	24-10-2007	Approved	N
Change in the name and/or address of the marketing authorisation for Italy and Sweden.	NL/H/0715/ 001/IA/006	IA	7-7-2008	21-7-2008	Approved	N
Change in the name of the medicinal product for Italy and Poland.	NL/H/0715/ 001/IB/007	IB	7-7-2008	6-8-2008	Approved	N
Change in batch size finished product.	NL/H/0715/ 001/II/008	II	11-12-2008	5-4-2009	Approved	N
Change in the shelf life of the finished product: as packaged for sale.	NL/H/0715/ 001/IB/009	IB	22-12-2008	21-1-2009	Approved	N
Change in the shelf life of the finished product: after dilution or reconstitution.	NL/H/0715/ 001/IB/010	IB	22-12-2008	21-1-2009	Approved	N
Implementation of agreed wording change(s) for which no new additional data are submitted.	NL/H/0715/ 001/IB/011	IB	11-10-2010	10-12-2010	Approved	N