

# **Public Assessment Report**

## **Decentralised Procedure**

### **Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion**

**Fludarabine Phosphate**

**UK/H/5290/001/DC**

**UK licence no: PL 30306/0442**

**Actavis Group PTC ehf**

## **LAY SUMMARY**

On 13<sup>th</sup> June 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) to Actavis Group PTC ehf. for the medicinal product Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion (PL 30306/0442; UK/H/5290/001/DC). This medicine is only available on prescription from your doctor.

Fludarabine Phosphate is an anti-cancer drug.

Fludarabine Phosphate is used to treat chronic B-cell lymphocytic leukaemia (B-CLL) in patients with sufficient healthy blood cell production. This is a type of cancer of white blood cells (the cells are called lymphocytes).

First treatment for chronic lymphocytic leukaemia with Fludarabine Phosphate should only be started in patients with advanced disease having disease related symptoms or evidence of disease progression.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of treatment with Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion outweigh the risks and a Marketing Authorisation was granted.

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## Module 1

Product Name	Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion
Type of Application	10(3), Hybrid application
Active Substance	Fludarabine Phosphate
Form	Concentrate for Solution for Injection or Infusion
Strength	25 mg/ml
MA Holder	Actavis Group PTC ehf. Reykjavíkurvegi 76-78 220 Hafnarfjörður Iceland
RMS	UK
CMSs	Austria, Bulgaria, Denmark, Estonia, Germany, Greece, Iceland, Italy, Latvia, Lithuania, Norway, Republic of Ireland, Romania, Spain, Sweden, Slovenia and The Netherlands
Procedure Number	UK/H/5290/001/DC
Timetable	Day 210: 25 <sup>th</sup> April 2013

## **Module 2**

### **Summary of Product Characteristics**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

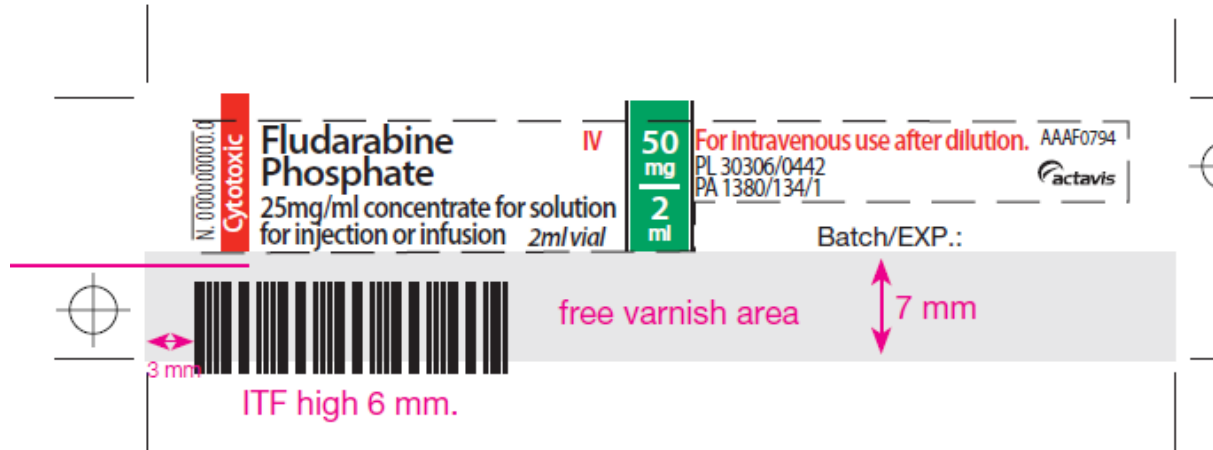
## **Module 3**

### **Patient Information Leaflet**

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

## Module 4

## Labelling









## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion in the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves could be approved.

This decentralised application concerns a hybrid application of a new pharmaceutical form of fludarabine phosphate (Fludarabine 25 mg/ml Concentrate for Solution for Injection or Infusion) submitted under Article 10(3) of Directive 2001/83/EC, as amended. The applicant cross-refers to Fludara<sup>®</sup> 50 mg Powder for Solution for injection or infusion, originally granted to Schering Healthcare Limited (PL 00053/0239) on 11<sup>th</sup> August 1994. The reference licence has undergone a Change of Ownership (CoA) procedure to Bayer Plc (PL 00010/0532) on 20<sup>th</sup> February 2008 followed by authorisation to the current Marketing Authorisation Holder, Genzyme Europe BV (PL 12375/0039) on 1<sup>st</sup> October 2009.

With UK as the RMS in this Decentralised Procedure (UK/H/5290/001/DC), Actavis Group PTC ehf. applied for the Marketing Authorisation for Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion in Austria, Bulgaria, Denmark, Estonia, Germany, Greece, Iceland, Italy, Latvia, Lithuania, Norway, Republic of Ireland, Romania, Spain, Sweden, Slovenia and The Netherlands.

Fludarabine phosphate is rapidly dephosphorylated to 2F-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2F-ara-ATP. This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase  $\alpha/\delta$  and  $\epsilon$ , DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur.

No new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being hybrid medicinal product of an originator product that has been licensed for over 10 years. The product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product. Thus, in accordance with the Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1\*\*), the applicant was not required to submit bioequivalence studies for this application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within and outside 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.

The applicant has provided a Summary of the Pharmacovigilance System and version 2.0 of

the Risk Management Plan (RMP). These are satisfactory.

All member states agreed to grant a licence for the above product at the end of the procedure (Day 210: 25<sup>th</sup> April 2013). After a subsequent national phase, the UK granted a licence for this product on 13<sup>th</sup> June 2013 (PL 30306/0442).

**II. ABOUT THE PRODUCT**

Name of the product in the Reference Member State	Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion
Name(s) of the active substance(s) (USAN)	Fludarabine Phosphate
Pharmacotherapeutic classification (ATC code)	Antineoplastic agents, purine analogues ATC code: L01B B05
Pharmaceutical form and strength(s)	Concentrate for Solution for Injection or Infusion
Reference number for the Decentralised Procedure	UK/H/5290/001/DC
Reference Member State	United Kingdom
Concerned Member States	Austria, Bulgaria, Denmark, Estonia, Germany, Greece, Iceland, Italy, Latvia, Lithuania, Norway, Republic of Ireland, Romania, Slovenia, Spain, Sweden and The Netherlands
Marketing Authorisation Number(s)	PL 30306/0442
Name and address of the authorisation holder	Actavis Group PTC ehf. Reykjavíkurvegi 76-78 220 Hafnarfjörður Iceland

### III SCIENTIFIC OVERVIEW AND DISCUSSION

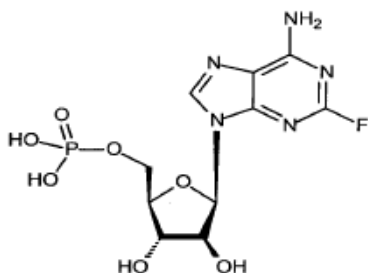
#### III.1 QUALITY ASPECTS

##### DRUG SUBSTANCE

INN: Fludarabine phosphate

Chemical Names: Fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl)-9H-purin-6-amine.

Structure:



Molecular formula: C<sub>10</sub>H<sub>13</sub>FN<sub>5</sub>O<sub>7</sub>P

Molecular weight: 365.2 g/mol

Appearance: White or almost-white, crystalline powder, hygroscopic.

Solubility: Slightly soluble in water, freely soluble in dimethylformamide, very slightly soluble in anhydrous ethanol.

Fludarabine phosphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance fludarabine phosphate are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

##### DRUG PRODUCT

###### Other Ingredients

Other ingredients consist of the pharmaceutical excipients disodium phosphate dihydrate, water for injections and sodium hydroxide (for pH adjustment).

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for the excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

###### Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain a stable product containing fludarabine phosphate which could be considered as a hybrid medicinal product of Fludara<sup>®</sup> 50 mg Powder for Solution for injection or infusion (Genzyme Europe BV).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.

### **Manufacture**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

### **Finished Product Specification**

The finished product specification is satisfactory. Test methods have been described and validated adequately. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

### **Container Closure System**

The finished product is supplied in a colourless glass vial (type I) with bromobutylic rubber stopper and metallic cap (aluminium) with polypropylene disk. Vials will be packed with or without a protective plastic overwrap. The pack size are 1 x 2 ml and 5 x 2 ml vials.

Specifications and Certificates of Analysis for the primary packaging materials have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years for unopened vials with storage condition, "Store between 2°C-8°C" has been set. This is satisfactory.

#### *After dilution:*

The diluted solution of Fludarabine Phosphate in 0.9% sodium chloride is stable for up to 28 days in PVC and PE bags at 2-8°C and at 25°C when protected from light. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

### **Bioequivalence/bioavailability**

No bioequivalence studies have been submitted and none are required to support applications of this type.

### **Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Fludarabine 50 mg powder for solution for injection or infusion (Actavis Group PTC EHF). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

The Marketing Authorisation holder has stated that not all packs are intended to be marketed. However, they have committed to submit mock-ups of any pack size to the relevant regulatory authorities before marketing.

### **Marketing Authorisation Application (MAA) Form**

The MAA form is satisfactory from a pharmaceutical perspective.

### **Expert Report (Quality Overall Summary)**

A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

### **Conclusion**

There are no objections to the approval of this product from a pharmaceutical point of view.

## **III.2 NON-CLINICAL ASPECTS**

### **PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY**

The pharmacological, pharmacokinetic and toxicological properties of fludarabine phosphate are well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Suitable justification has been provided for the non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

## **III.3 CLINICAL ASPECTS**

### ***Pharmacokinetics***

In accordance with Note for Guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence studies have been submitted with this application and none are required.

No other new data have been submitted and none are required for applications of this type.

### ***Pharmacodynamics***

No new data have been submitted and none are required for applications of this type.

### ***Clinical efficacy***

No new data have been submitted and none are required for applications of this type.

### ***Clinical safety***

Fludarabine phosphate has an acceptable adverse event profile. No new safety data were supplied or required for this hybrid application. Fludarabine phosphate has a well-established side-effect profile and is generally well-tolerated.

***Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling***

The SmPC, PIL and labelling are satisfactory from a clinical perspective and consistent with those for the reference product.

***Clinical Expert Report***

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

***Marketing Authorisation Application (MAA) Form***

The MAA form is satisfactory from a clinical perspective.

***Clinical Conclusion***

There are no objections to the approval of this product from a clinical point of view.



#### **IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

##### **QUALITY**

The important quality characteristics of Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion 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.

##### **NON-CLINICAL**

No non-clinical data were submitted and none are required for applications of this type.

##### **CLINICAL**

No new efficacy data were submitted and none are required for applications of this type. As the safety profile of fludarabine phosphate is well-known, no additional data were required.

##### **SAFETY**

No new or unexpected safety concerns arose from this application.

##### **PRODUCT LITERATURE**

The SmPC, PIL and labelling are satisfactory.

##### **BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fludarabine phosphate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome