COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fludarabinefosfaat Accord 25 mg/ml, concentrate for solution for injection or infusion

(fludarabine phosphate)

NL/H/4563/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Fludarabinefosfaat Accord 25 mg/ml, concentrate for solution for injection or infusion. The procedure was finalised in the United Kingdom (UK/H/5564/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Public Assessment Report

Decentralised Procedure

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

Fludarabine Phosphate

UK/H/5564/001/DC

UK licence no: PL 20075/0379

Accord Healthcare Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY
Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion
(Fludarabine phosphate)

This is a summary of the public assessment report (PAR) for Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion (PL 20075/0379). It explains how Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion 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 Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion.

For practical information about using Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion and what is it used for?

Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is a 'generic medicine'. This means that this medicine is similar to a 'reference medicine' already authorised in the UK called Fludara® 50 mg Powder for Solution for injection or infusion (Genzyme Europe BV; PL 12375/0039).

Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is used in the treatment of B-cell chronic lymphocytic leukaemia (B-CLL) in patients with sufficient healthy blood cell production. First treatment for chronic lymphocytic leukaemia with this medicine should only be started in patients with advanced disease having disease-related symptoms or evidence of disease progression.

How is Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion used?

Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is given intravenously (into a vein). This medicinal product should be administered under the supervision of a qualified doctor experienced in the use of anti-cancer therapy.

The dosage depends on patients' body surface area. This is measured in square metres (m^2) and is worked out by a doctor from the height and weight of the patient. The recommended dose is 25 mg fludarabine phosphate/m^2 body surface area. The dose will be given once a day for 5 consecutive days. This 5-day course of treatment will be repeated every 28 days until a doctor decides that the best effect has been achieved (usually after 6 courses).

The duration of the treatment depends on how successful the treatment is and how well the patient's tolerance is to this medicine. The repeat course may be delayed if side effects are a problem. Patients will have regular blood tests during the treatment and the dosage will be carefully adjusted according to the number of blood cells and response to the therapy. The dosage may be decreased if side effects are a problem.

Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is not recommended for use in children.

This medicine can only be obtained on prescription from a doctor.

For further information on how Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How does Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion work?

Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion contains the active substance fludarabine phosphate, which belongs to a group of medicines called antineoplastic agents. This medicine stops the growth of new cancer cells.

How has Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion been studied?

As this product is a concentrate for solution for injection or infusion, the applicant has not performed any bioequvalence studies. No additional studies were needed as Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is a generic medicine that is given intravenously and contains the same active substance and content as the reference medicine, Fludara® 50 mg Powder for Solution for injection or infusion (Genzyme Europe BV; PL 12375/0039).

What are the benefits and risks of Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion?

As Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is a generic medicine and is comparable to the reference medicine (Fludara® 50 mg Powder for Solution for injection or infusion), its benefits and risks are taken as being the same as those of Fludara® 50 mg Powder for Solution for injection or infusion (Genzyme Europe BV; PL 12375/0039).

Why is Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion approved?

No new or unexpected safety concerns arose from this application. It was, therefore, concluded that the benefits of Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion outweigh the identified risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion?

A risk management plan has been developed to ensure that Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion

Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Republic of Ireland, Spain, Sweden, The Netherlands and the UK agreed to grant a Marketing Authorisation for Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion on 8th August 2014. A Marketing Authorisation was granted in the UK on 4th September 2014 (PL 20075/0379).

The full PAR for Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion follows this summary. For more information about treatment with Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2014.

TABLE OF CONTENTS

Module 1

Information about initial procedure

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	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom
RMS	UK
CMSs	Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Republic of Ireland, Spain, Sweden and The Netherlands
Procedure Number	UK/H/5564/001/DC
Timetable	Day 173: 8th August 2014

Module 2
Summary of Product Characteristics

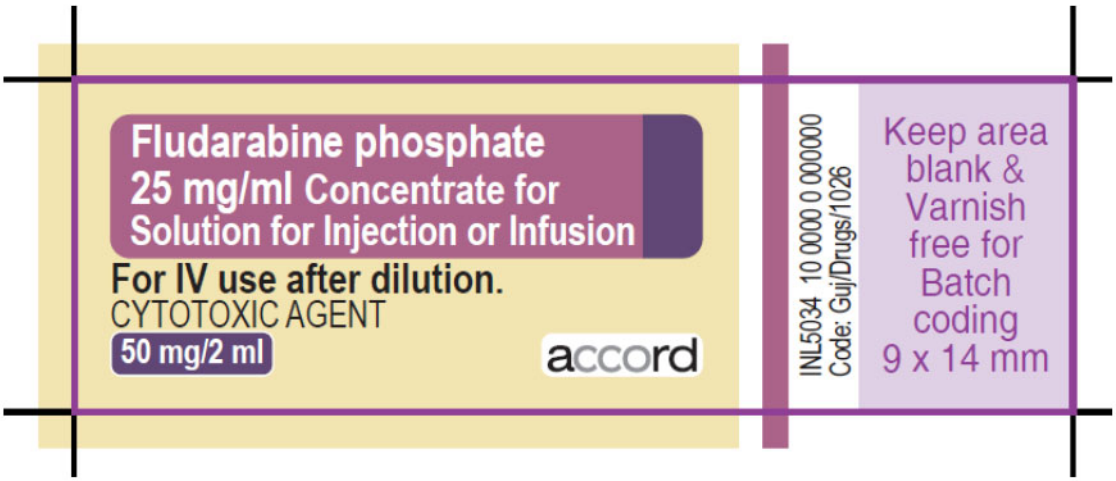
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

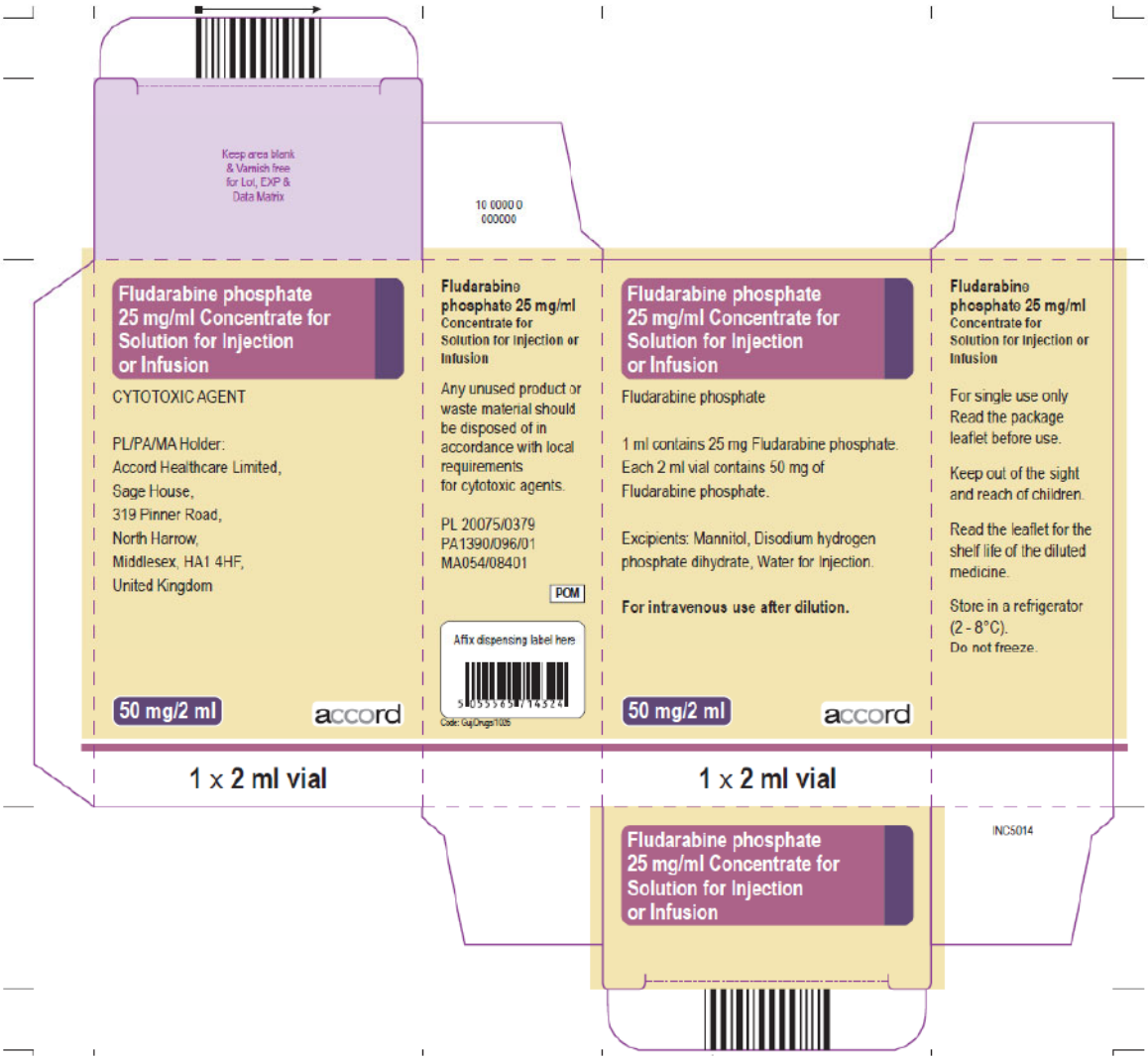
Module 3
Patient Information Leaflet

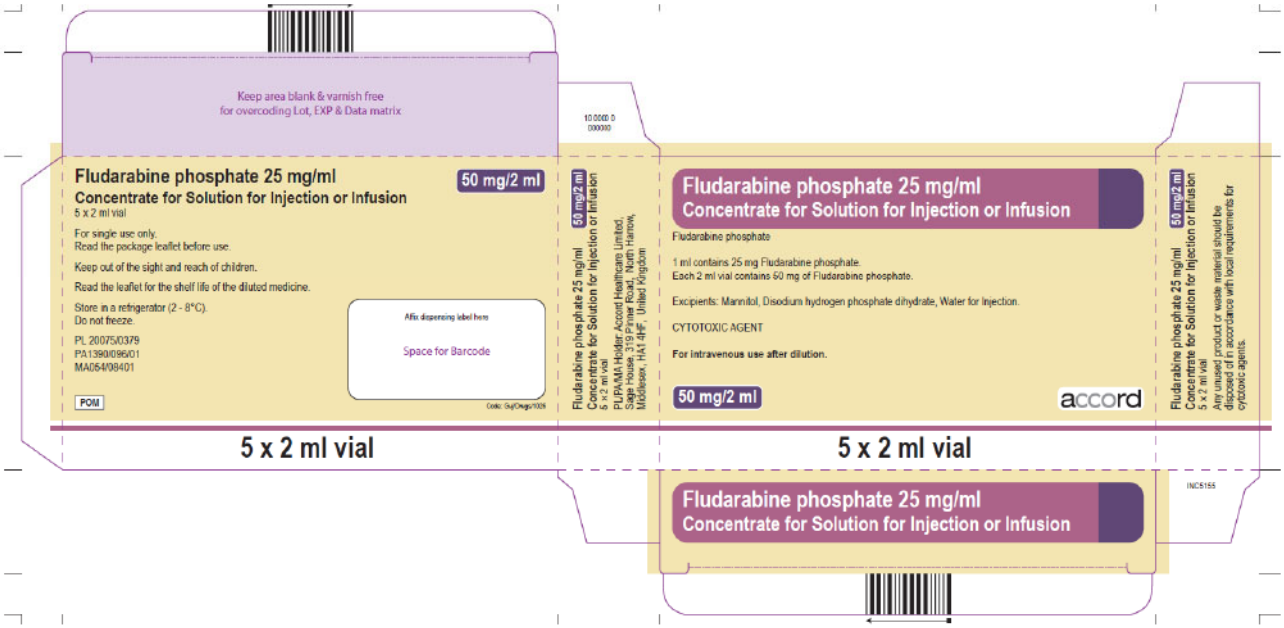
In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

Labelling






Keep area blank & varnish free
for overcoding Lot, EXP & Data matrix
Fludarabine phosphate 25 mg/ml
Concentrate for Solution for Injection or Infusion
5 x 2 ml vial
50 mg/2 ml
For single use only.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Read the leaflet for the shelf life of the diluted medicine.
Store in a refrigerator (2 - 8°C).
Do not freeze.
PL 20075/0379
PA1390/095/01
MA054/08401
POM
Affix dispensing label here
Space for Barcode
5 x 2 ml vial
Fludarabine phosphate 25 mg/ml
Concentrate for Solution for Injection or Infusion
Fludarabine phosphate
1 ml contains 25 mg Fludarabine phosphate.
Each 2 ml vial contains 50 mg of Fludarabine phosphate.
Excipients: Mannitol, Disodium hydrogen phosphate dihydrate, Water for Injection.
CYTOTOXIC AGENT
For intravenous use after dilution.
50 mg/2 ml
accord
5 x 2 ml vial
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.


Keep area blank & varnish free
for overcoding Lot EXP & Data matrix
120 x 25 mm
Fludarabine phosphate 25 mg/ml
Concentrate for Solution for Injection or Infusion
Fludarabine phosphate 25 mg/ml
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PL/PA/MA Holder:
Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
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CYTOTOXIC AGENT
For intravenous use after dilution.
50 mg/2 ml
accord
10 x 2 ml vial
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

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 (PL 20075/0379; UK/H/5564/001/DC) in the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves, is approvable.

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

With UK as the RMS in this Decentralised Procedure (UK/H/5564/001/DC), Accord Healthcare Limited, applied for the Marketing Authorisation for Fludarabine Phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion in Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Republic of Ireland, Spain, Sweden 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 α/δ and ε, 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/Corr**), 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 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.

For manufacturing sites outside the community, the RMS has accepted copies of current

GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

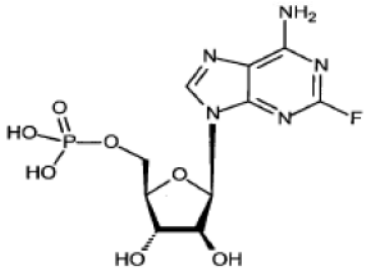
All member states agreed to grant a licence for the above product at the end of the procedure (Day 173: 8th August 2014). After a subsequent national phase, the UK granted a licence for this product on 4th September 2014 (PL 20075/0379).

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/5564/001/DC
Reference Member State	United Kingdom
Concerned Member States	Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Republic of Ireland, Spain, Sweden and The Netherlands.
Marketing Authorisation Number(s)	PL 20075/0379
Name and address of the authorisation holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

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: $C_{10}H_{13}FN_5O_7P$
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 and Healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients mannitol, disodium hydrogen phosphate dihydrate and Water for injection.

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these 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® 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 scale batches have been provided. The results are satisfactory.

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

Container Closure System
The finished product is supplied in a glass vial (type I) with fluorotec rubber stopper and an aluminium flip-off cap. The 2 ml-vials contain 50 mg fludarabine phosphate and are supplied in packs of 1, 5 and 10 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 conditions "Store in a refrigerator (2 - 8°C)" and "Do not freeze" have been set. These are satisfactory.

Chemical and physical in-use stability has been demonstrated at 0.2 mg/ml & 6.0 mg/ml after dilution with 0.9% Sodium chloride and 5% Glucose Injection for 7 days at 2-8 °C and 5 days at 20 – 25 °C in non-PVC bags and Glass bottles.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should 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 PILs for Zoledronic Acid 4 mg/5ml powder for solution for infusion. In addition, the bridging report provides a comparison to the information approved in the PIL for Fludara 50 mg powder for solution for injection or infusion. 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.

A suitable justification has been provided for not submitting 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/Corr**), bioequivalence studies are 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.

Pharmacovigilance System and Risk Management Plan

The applicant has provided a summary of pharmacovigilance system and a detailed Risk Management Plan (RMP) with this application. These are satisfactory**.**

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.

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 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