COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cytarabine Accord 100 mg/ml, solution for injection or infusion

(cytarabine)

NL/H/4561/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Cytarabine Accord 100 mg/ml, solution for injection or infusion. The procedure was finalised in the United Kingdom (UK/H/1641/001/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

Cytarabine 100mg/ml Solution for Injection or Infusion

UK/H/1641/001/DC
UK licence no: PL 20075/0121

Accord Healthcare Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Cytarabine 100mg/ml Solution for Injection or Infusion (PL 20075/0121). This prescription-only medicine (POM) is used in the in the treatment of acute myeloid leukaemia in adults and for other acute leukaemias.

Cytarabine Injection/Infusion contains the active ingredient cytarabine. Cytarabine is one of a group of medicines known as cytotoxics; these medicines are used in the treatment of acute leukaemias (cancer of blood where you have too many white blood cells). Cytarabine interferes with the growth of cancer cell, which are eventually destroyed.

The test product was considered to be the same as the reference product Cytarabine 100mg/ml Injection (PL 00032/0198), first licensed in the UK in June 1999 to Pharmacia Limited.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Cytarabine 100mg/mlSolution for Injection or Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Cytarabine 100mg/ml solution for injection or infusion
Type of Application	Generic, Article 10.1
Active Substance	Cytarabine
Form	Solution For Injection or infusion
Strength	100mg/ml
MA Holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, Harrow, Middlesex HA1 4HF UK
RMS	UK
CMS	Bulgaria, Estonia, Latvia and Lithuania.
Procedure Number	UK/H/1641/001/DC
End of Procedure	16th November 2009

Module 2
Summary of Product Characteristics

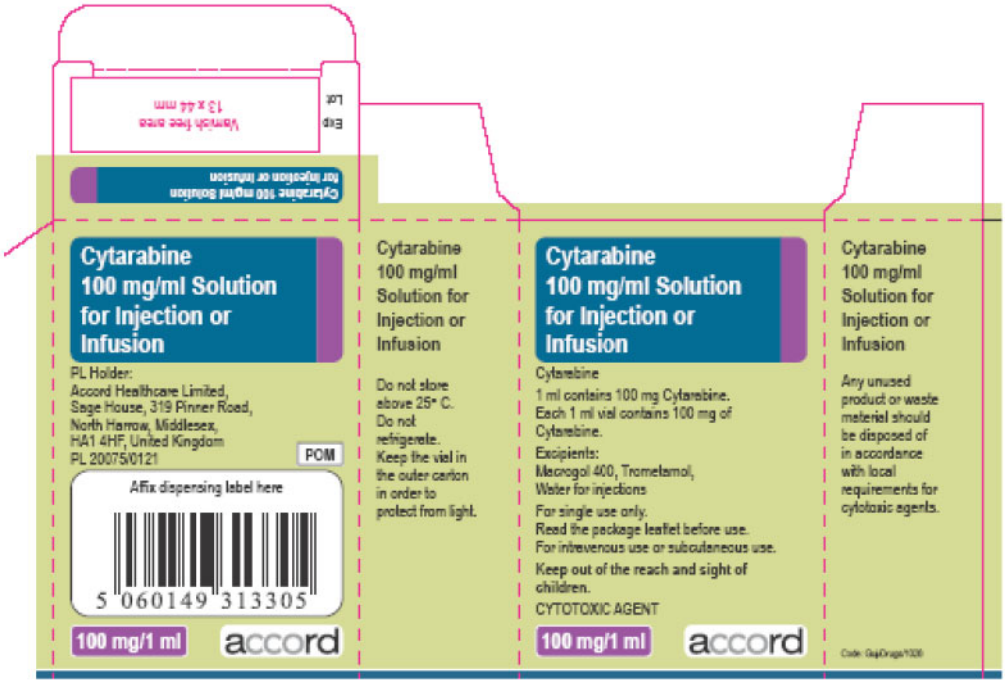
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

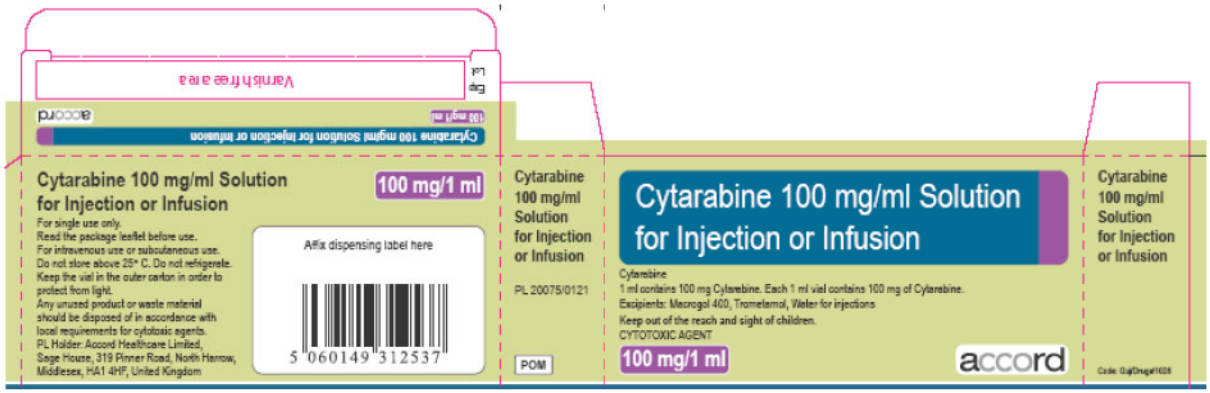
Module 3
Product Information Leaflet

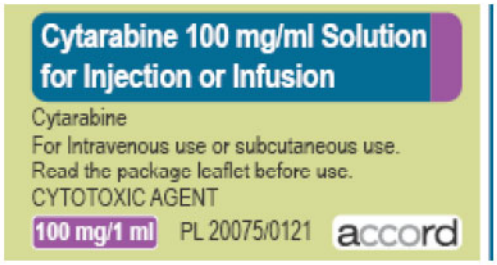
In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

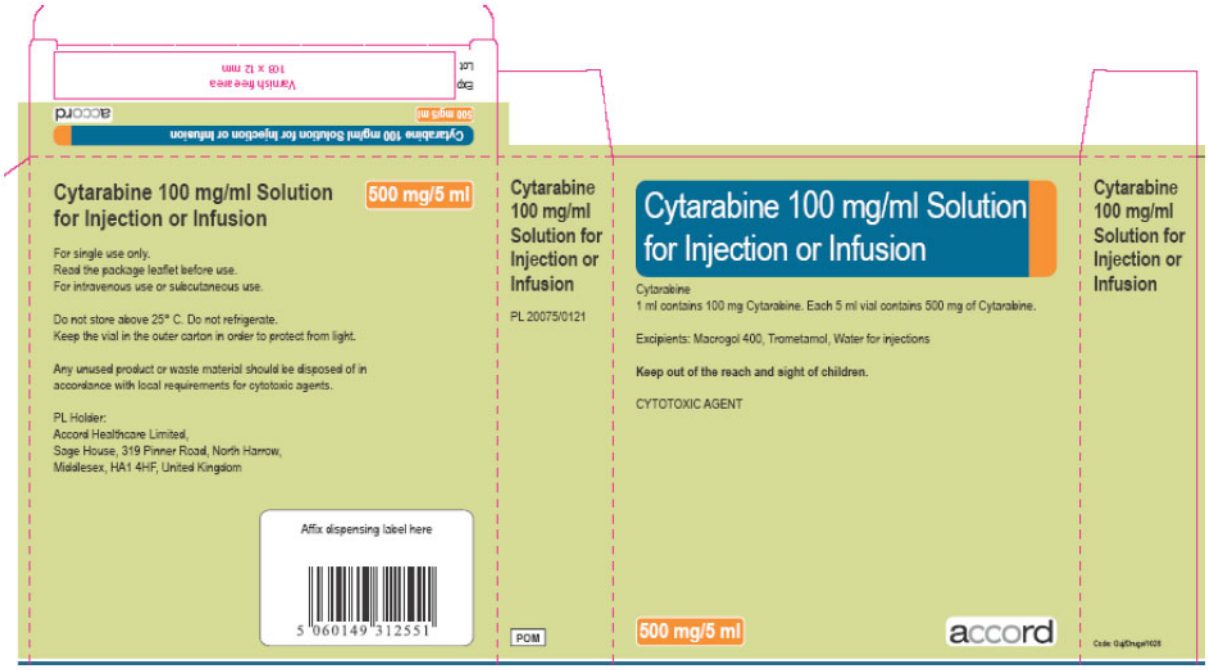
Module 4
Labelling

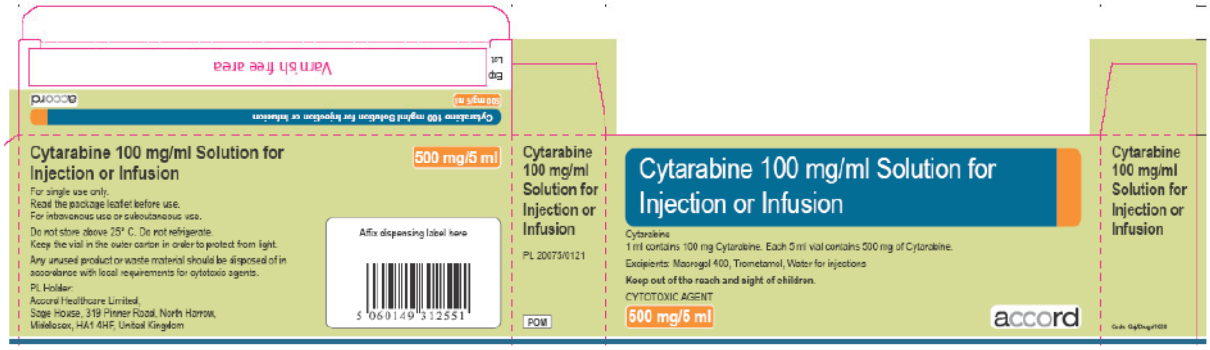
Cytarabine 100mg/ml Solution for Injection or Infusion








Cytarabine 100 mg/ml Solution for Injection or Infusion
500 mg/5 ml
For single use only.
Read the package leaflet before use.
For intravenous use or subcutaneous use.
Do not store above 25° C. Do not refrigerate.
Keep the vial in the outer carton in order to protect from light.
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.
PL Holder:
Accord Healthcare Limited,
Sage House, 319 Pinner Road, North Harrow,
Middlesex, HA1 4HF, United Kingdom
Affix dispensing label here
5 060149 312551
POM
Cytarabine 100 mg/ml Solution for Injection or Infusion
PL 20075/0121
Cytarabine 100 mg/ml Solution for Injection or Infusion
Cytarabine
1 ml contains 100 mg Cytarabine. Each 5 ml vial contains 500 mg of Cytarabine.
Excipients: Macrogol 400, Trometamol, Water for injections
Keep out of the reach and sight of children.
CYTOTOXIC AGENT
500 mg/5 ml
accord
Cytarabine 100 mg/ml Solution for Injection or Infusion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Do not store above 25° C. Do not refrigerate.
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Accord Healthcare Limited,
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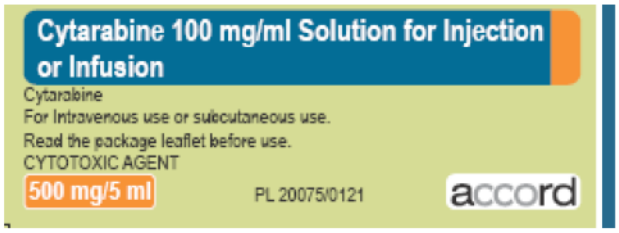
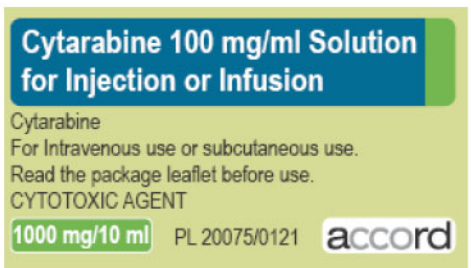
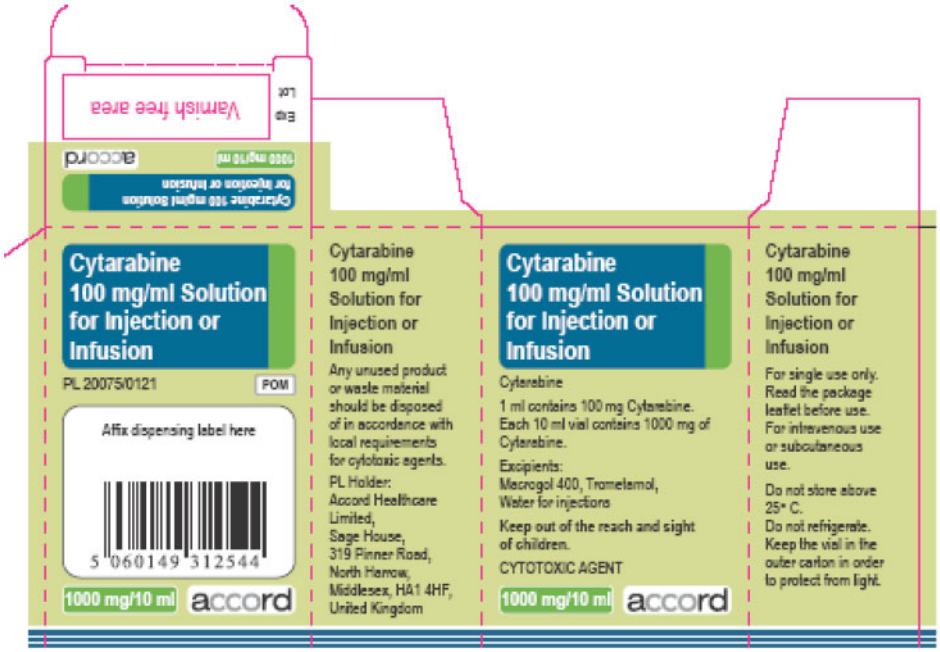

Cytarabine 100 mg/ml Solution for Injection or Infusion
Cytarabine
For Intravenous use or subcutaneous use.
Read the package leaflet before use.
CYTOTOXIC AGENT
500 mg/5 ml
PL 20075/0121
accord


Cytarabine 100 mg/ml Solution for Injection or Infusion
Cytarabine
For Intravenous use or subcutaneous use.
Read the package leaflet before use.
CYTOTOXIC AGENT
1000 mg/10 ml
PL 20075/0121
accord


Varnish free area
Exp
Lot
accord
1000 mg/10 ml
Cytarabine 100 mg/ml Solution for Injection or Infusion
Cytarabine
100 mg/ml Solution for Injection or Infusion
PL 20075/0121
POM
Affix dispensing label here
5 060149 312544
1000 mg/10 ml
accord
Cytarabine
100 mg/ml Solution for Injection or Infusion
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.
PL Holder:
Accord Healthcare Limited,
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom
Cytarabine
100 mg/ml Solution for Injection or Infusion
Cytarabine
1 ml contains 100 mg Cytarabine.
Each 10 ml vial contains 1000 mg of Cytarabine.
Excipients:
Macrogol 400, Trometamol, Water for injections
Keep out of the reach and sight of children.
CYTOTOXIC AGENT
1000 mg/10 ml
accord
Cytarabine
100 mg/ml Solution for Injection or Infusion
For single use only.
Read the package leaflet before use.
For intravenous use or subcutaneous use.
Do not store above 25° C.
Do not refrigerate.
Keep the vial in the outer carton in order to protect from light.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Cytarabine 100mg/ml Solution for Injection or Infusion, used in the treatment of acute myeloid leukaemia in adults and for other acute leukaemias, is approvable.

This is an application submitted under Article 10(1) of Directive 2001/83 (as amended) for Cytarabine 100mg/ml Solution for Injection. It has been shown to be a generic medicinal product of the originator product Cytarabine 100mg/ml Solution for Infusion or Injection (Marketing Authorisation Holder: Pharmacia Limited) which was granted a licence in the UK on 3rd June 1999; hence the 10 year rule is fulfilled.

Cytarabine is a pyrimidine nucleoside and S-phase specific antineoplastic agent, which inhibits the synthesis of deoxyribonucleic acid. Cytarabine is metabolised by deoxycytidine kinase to 5'- mononucleotide (AraCMP). Detailed studies on the mechanism of cytotoxicity in vitro suggest that the primary action of Cytarabine is inhibition of deoxycytidine synthesis. Inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions. In light of the S-phase specificity, the drug is highly sequence-dependent and may be given either by continuous infusion or intermittently. Cytarabine is commonly used to treat AML. Side effects include myelosuppression, nausea, hyperuricaemia, neurotoxicity, The Cytarabine Syndrome and stomatitis.

The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

A formal *Environment Assessment* was not submitted. This is acceptable as no increase in environmental risk is to be expected compared to that of the reference product.

No *Risk Management Plan* other than the documentation of the PharmacoVigilance system has been provided. The Applicant has supplied a justification for not submitting a European Risk Management Plan and this is satisfactory.

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.

Since a literature review has been presented for the Non-clinical Overview, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

No new clinical study was submitted.

The patient information leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Cytarabine 100mg/ml Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Cytarabine
Pharmacotherapeutic classification (ATC code)	L01BC01: Pyrimidine analogue
Pharmaceutical form and strength(s)	100 mg/ml solution for injection or infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/1641/001/DC
Reference Member State	United Kingdom
Member States concerned	Bulgaria, Estonia, Latvia and Lithuania
Marketing Authorisation Number(s)	PL 20075/0121
Name and address of the authorisation holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex HA1 4HF UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

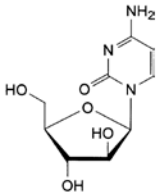
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Cytarabine

General Information
Nomenclature
Name: Cytarabine

Structure



Description: White or almost white crystalline powder
Molecular formula: $C_9H_{13}N_3O_5$
Relative molecular mass: 243.22
There is a Ph Eur monograph for the drug substance, cytarabine.

Manufacture
A satisfactory Ph Eur Certificate of Suitability (CEP) has been provided which covers the manufacture and control of the drug substance cytarabine. Additional tests for related substances and residual solvents have been described and are in line with ICH guidelines.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Cytarabine drug substance is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data have been provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

The finished product manufacturer routinely tests each batch of the drug substance in accordance with a satisfactory specification upon receipt.

Appropriate stability data have been generated for the drug substance and supports an appropriate retest period when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely macrogol 400, trometamol and water for injections. An appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph.Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

There were no novel excipients used and no overages.

Pharmaceutical Development
The objective of development activities was to achieve a stable formulation of cytarabine 100mg/ml similar to the reference product cytarabine 100mg/ml, manufactured by Pharmacia Limited.

Compatibility
Compatibility studies have demonstrated that the product is compatible with the proposed packaging component and rubber stoppers. Container integrity is demonstrated and is satisfactory.

Impurity Profiles
Comparative impurity profiles between the test product and a German authorised product 'ARA-cell', which is equivalent to the UK reference product, have been provided and are satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data for two commercial batches have been provided which are satisfactory. All data are within specifications.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. 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 filled into colourless neutral Type I glass vials and sealed with chlorobutyl rubber stopper with aluminium flip-off seals.

For 1 ml,
Solution for injection is filled in 2 ml Type - I clear glass vial closed with 13 mm grey rubber stopper and 13 mm aluminium flip-off transparent blue seal with pack sizes of 1x1ml vial, 5x1ml vials.

For 5 ml,
Solution for injection is filled in 5 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal with pack sizes of 1x5ml vial and 5x5ml vial.

For 10 ml,
Solution for injection is filled in 10 ml Type - I clear tubular glass vial closed with 20 mm grey rubber stopper and 20 mm aluminium flip-off transparent blue seal in pack size of 1 x 10ml vials.

All primary product packaging complies with EU legislation regarding contact with food.

Satisfactory specifications and certificates of analysis are provided. Satisfactory declaration has been provided by the suppliers of all packaging materials comply with the EC Directed 2002/72 as well as with the relevant Ph Eur monograph for containers.

Stability
Stability studies were performed on three batches of each presentation of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years for unopened product with the storage conditions "Do not store above 25° C", "Keep the vial in the outer carton in order to protect from light" and "Do not refrigerate".

The shelf-life of the injection *in-use* is "Chemical and physical in-use stability has been demonstrated in sodium chloride injection (0.9 % w/v) and dextrose injection (5% w/v) for up to 24 hours at temperature below 25° C and for up to 72 hours at 2-8°C".

General storage conditions for the product in use are "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 would normally not be longer than 24 hours at 2-8° C, unless dilution has taken place in controlled and validated aseptic conditions".

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic product of the proposed and originator products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and reference products.

2 NON-CLINICAL ASSESSMENT

2.1. Critical evaluation of the Non-Clinical Overview

The pharmacological, pharmacokinetic and toxicological properties of cytarabine are well known. As cytarabine is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a suitably qualified person. The overview cites 58 references from the published literature dated up to 2007 and is satisfactory.

2.2 Conclusions

There are no objections to approval of Cytarabine Injection 100mg/ml solution for injection or infusion.

III.3 CLINICAL ASPECTS
INTRODUCTION

Cytarabine is a pyrimidine nucleoside and S-phase specific antineoplastic agent, which inhibits the synthesis of deoxyribonucleic acid. Cytarabine is metabolised by deoxycytidine kinase to 5'- mononucleotide (AraCMP). Detailed studies on the mechanism of cytotoxicity in vitro suggest that the primary action of Cytarabine is inhibition of deoxycytidine synthesis. Inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions. In light of the S-phase specificity, the drug is highly sequence-dependent and may be given either by continuous infusion or intermittently. Cytarabine is commonly used to treat AML. Side effects include myelosuppression, nausea, hyperuricaemia, neurotoxicity, The Cytarabine Syndrome and stomatitis.

Therapeutic Indications
Cytotoxic. For induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children

The proposed indications are consistent with the approved UK reference SmPC.

Posology and method of administration
By intravenous infusion or injection, or subcutaneous injection.

Cytarabine should not be administered by the intrathecal route.

Dosage recommendations may be converted from those in terms of bodyweight to those related to surface area by means of nomograms.

1. Remission induction:
a) Continuous treatment:

i) Rapid injection - 2 mg/kg/day is a judicious starting dose. Administer for 10 days. Obtain daily blood counts. If no antileukaemic effect is noted and there is no apparent toxicity, increase to 4 mg/kg/day and maintain until therapeutic response or toxicity is evident. Almost all patients can be carried to toxicity with these doses.
ii) 0.5 - 1.0 mg/kg/day may be given in an infusion of up to 24 hours duration. Results from one-hour infusions have been satisfactory in the majority of patients. After 10 days this initial daily dose may be increased to 2 mg/kg/day subject to toxicity. Continue to toxicity or until remission occurs.

b) Intermittent treatment:
3-5 mg/kg/day are administered intravenously on each of five consecutive days. After a two to nine-day rest period, a further course is given. Continue until response or toxicity occurs.

The first evidence of marrow improvement has been reported to occur 7 - 64 days (mean 28 days) after the beginning of therapy.

In general, if a patient shows neither toxicity nor remission after a fair trial, the cautious administration of higher doses is warranted. As a rule, patients have been seen to tolerate higher doses when given by rapid intravenous injection as compared with slow infusion. This

difference is due to the rapid metabolism of Cytarabine and the consequent short duration of action of the high dose.

2. Maintenance therapy:
Remissions, which have been induced by Cytarabine, or by other drugs, may be maintained by intravenous or subcutaneous injection of 1 mg/kg once or twice weekly.

Children:
Children appear to tolerate higher doses than adults and, where dose ranges are quoted, the children should receive the higher dose and the adults the lower.

Elderly Patients:
There is no information to suggest that a change in dosage is warranted in the elderly. Nevertheless, the elderly patient does not tolerate drug toxicity as well as the younger patient, and particular attention should thus be given to drug induced leucopenia, thrombocytopenia, and anaemia, with appropriate initiation of supportive therapy when indicated.

The proposed posology is consistent with the approved UK reference SmPC.

The clinical overview report covers the product rationale, overview of biopharmaceutics, pharmacology, efficacy, safety and benefits and risks conclusions and is written by a suitably qualified expert. The report refers to 64 publications up to the year 2008.

3.2 Clinical study reports
No new data have been submitted and none are required for this generic application.

Cytarabine 100 mg/ml solution for injection or infusion is the generic version of Cytarabine 100 mg/ml solution for injection (Pharmacia, UK). The use of the reference product is well-established in the EU. .

According to CPMP guidelines, the Applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

3.2.1 Pharmacodynamic studies
No new data have been submitted and none are required for this application.

The pharmacodynamic and pharmacokinetic claims in the SmPC are consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties have been extensively studied in the past.

3.2.2 Additional data
Cytarabine is indicated for induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.

Satisfactory evidence to support the proposed indication has been provided in the clinical overview (e.g. Yee et al., 2004; Bahng H et al., 2001; Palmieri S et al., 2002).

Cytarabine has an acceptable adverse events profile. No novel safety data are supplied or required for this generic application. The Applicant has provided a review of the published literature, confirming the safety of Cytarabine (HSDB: Hazardous Substance Data Bank: National Library of Medicine).

4 Post marketing experience

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

Cytarabine has a well-recognised efficacy and an acceptable level of safety in the indications approved for the reference product, and corresponding products have been widely used in many countries.

5 Benefit-Risk assessment

The application contains an adequate review of published clinical data. Approval is recommended from the clinical point of view.

Summary of Product Characteristics

This is satisfactory.

Patient Information Leaflet and Labels

These are satisfactory.

CONCLUSIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Cytarabine 100mg/ml Solution for Injection or Infusions 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
07/01/2010	Information Update	Information update created as changes were made to the dimensions of the labelling mock-ups	Approved
15/05/2013	Type IB	To update sections 2, 3, 4.1 - 4.6, 4.8, 4.9, 5.1, 5.2, 6.1 - 6.4 and 6.6 of the SPC and the PIL to bring it in line with recently approved SmPC and PIL of Cytarabine 100 mg/ml solution for injection or infusion (Fresenius Kabi Oncology Plc; UK/H/4353/001/DC).	Approved 10/01/2014

Annex 1

Reference: PL 20075/0121 - 0016
Product: Cytarabine 100 mg/ml solution for Injection or Infusion
Marketing Authorisation Holder: Accord Healthcare Limited
Active Ingredient(s): Cytarabine

Reason:
To update sections 2, 3, 4.1 - 4.6, 4.8, 4.9, 5.1, 5.2, 6.1 - 6.4 and 6.6 of the SPC and the PIL to bring it in line with recently approved SmPC and PIL of Cytarabine 100 mg/ml solution for injection or infusion (Fresenius Kabi Oncology Plc; UK/H/4353/001/DC).

Supporting Evidence
A revised SmPC and PIL have been provided. The currently approved labelling is acceptable and needs no further revisions.

Evaluation
The amended sections of the SmPC and the amended PIL are satisfactory.

The current approved UK versions of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.

Decision
Approved on 10 January 2014.