23 July 2020
EMA/CHMP/411838/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Arsenic trioxide medac

International non-proprietary name: arsenic trioxide

Procedure No. EMEA/H/C/005218/0000

Note

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

Administrative information

Name of the medicinal product:	Arsenic trioxide medac
Applicant:	medac Gesellschaft für klinische Spezialpräparate mbH Theaterstrasse 6 22880 Wedel GERMANY
Active substance:	ARSENIC TRIOXIDE
International non-proprietary name/Common name:	arsenic trioxide
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, other antineoplastic agents (L01XX27)
Therapeutic indication(s):	Arsenic trioxide medac is indicated for induction of remission, and consolidation in adult patients with: • Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-*trans*-retinoic acid (ATRA) • Relapsed/refractory APL (Previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	1 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	10 vials

Table of contents

List of abbreviations

APL	Acute Promyelocytic Leukaemia
BP	British Pharmacopeia
CHMP	the Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
F_{pen}	Fraction of market penetration
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma optical emission spectrometry
K_{ow}	n-octanol/water partition coefficient
LoQ	List of Questions
PEC	Predicted Environmental Concentration
PBT	Persistent, Bioaccumulative and Toxic
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
SmPC	Summary of Product Characteristics
vPvB	Very Persistent and Very Bioaccumulative
USP	United States Pharmacopoeia
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant medac Gesellschaft für klinische Spezialpräparate mbH submitted on 26 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Arsenic trioxide medac, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Arsenic trioxide medac is indicated for induction of remission, and consolidation in adult patients with:

- Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-*trans*-retinoic acid (ATRA)
- Relapsed/refractory APL (Previous treatment should have included a retinoid and chemotherapy)

characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and literature references instead of non-clinical and clinical unless justified otherwise

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Trisenox 1 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Teva B.V.
- Date of authorisation: 05-03-2002
  - Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/02/204/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Trisenox 1 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Teva B.V.

- Date of authorisation: 05-03-2002
  - Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/02/204/001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Milena Stain

The application was received by the EMA on	26 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 March 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	30 April 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP	14 May 2020

during the meeting on	
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Arsenic trioxide medac on	23 July 2020
The CHMP adopted a report on similarity of Arsenic Trioxide medac with Dacogen, Mylotrag, Vyxeos, Rydapt, Xospata, and Daurismo	23 July 2020

2. Scientific discussion

2.1. Introduction

This application is for marketing authorisation of Arsenic trioxide medac 1 mg/ml concentrate for solution for infusion and is based on Directive 2001/83/EC Article 10 (1): a generic application, referring to the reference Trisenox 1 mg/ml concentrate for solution for infusion of Teva B.V. which has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA. Trisenox 1 mg/ml concentrate for solution for infusion was first authorised within the EU on the 05-03-2002 under registration number EU/1/02/204/001.

The mechanism of action of arsenic trioxide is not completely understood. Arsenic trioxide causes morphological changes and deoxyribonucleic acid (DNA) fragmentation characteristic of apoptosis in NB4 human promyelocytic leukaemia cells in vitro. Arsenic trioxide also causes damage or degradation of the fusion protein Pro-Myelocytic Leukaemia/Retinoic Acid Receptor-alpha (PML/RAR alpha).

The reference product Trisenox is indicated as a monotherapy or in combination with other anticancer products in treatment of acute promyelocytic leukaemia (APL). The currently approved indication for Trisenox is as follows:

TRISENOX is indicated for induction of remission, and consolidation in adult patients with:

- Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA)
- Relapsed/refractory APL (previous treatment should have included a retinoid and chemotherapy)

characterised by the presence of the t(15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 1 mg/ml of arsenic trioxide.

Other ingredients are sodium hydroxide, hydrochloric acid (as pH adjusters), and water for injections.

The product is available in a type I glass vial with a chlorobutyl rubber stopper, an aluminium shell and a plastic flip-off button as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of arsenic trioxide is Arsenic (III) oxide corresponding to the molecular formula As_2O_3. It has a relative molecular mass of 197.84 g/mol and the following structure:

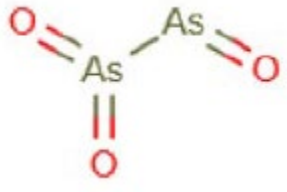

Figure 1: Active substance structure

The solid-state properties of the active substance were measured by a combination of crystallography (XRD) for characterization of the cubic crystal form, thermogravimetric analysis, hygroscopy, and IR spectroscopy.

The active substance is a non-hygroscopic white to off white crystalline powder, practically insoluble to sparingly soluble in water. It dissolves in solutions of alkali hydroxides (1M NaOH) but is less soluble in acids. It is practically insoluble in ethanol, chloroform and ethyl ether.

Arsenic trioxide has a non-chiral molecular structure. Polymorphism has been observed. The cubic crystal form is used.

Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesized in 3 main steps using commercially available well-defined starting materials with acceptable specifications. The specifications and control methods for starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in white opaque high-density polyethylene bottles with blue polypropylene closure containing a lid of polyethylene foam which complies with the Ph. Eur. Monographs, and the EC 10/2011 as amended.

Specification

The active substance specification from the finished product manufacturer includes tests for appearance (visual), identification (Ph. Eur.), appearance of the solution (Ph. Eur.), pH of solution (Ph. Eur.), assay (potentiometric titration), heavy metals (ICP-OES), iron (ICP-OES), As(0) content (ion chromatography), As_2O_5 content (ion chromatography), water content (coulometry), microbial enumeration (Ph. Eur.), and endotoxins (Ph. Eur.).

The validation data of the ICP-OES method to test metallic arsenic is currently not available, due to social distancing practice in the lab as a result of COVID-19 and the method validation and report cannot be completed by the time of the opinion. However, an appropriate method description for the ICP-OES analytical method for determination of metallic arsenic (As0) is provided. The CHMP recommended to provide the validation data of the ICP-OES method to test metallic arsenic together with the next variation. Impurities are not present at higher than the qualification threshold according to ICH Q3A. Appropriate specifications have been set.

The controls that are currently associated with the active substance process ensure that the levels of potential elemental impurities are maintained below their respective PDEs as established for the parenteral route of administration in the finished product.

The analytical methods used have been adequately described or referenced, where relevant, and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (3 commercial scale batches) for the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long-term conditions (25ºC / 60% RH and 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The tests and analytical methods used were the same as for release and are stability indicating.

All results comply with the specification. The long-term data and accelerated data show no changes over time and only little variability. Based on this data, an extrapolation of the retest period beyond the period covered by long term data is proposed according to ICH Q1E "Note for guidance on evaluation of stability data" and it is acceptable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months if it is preserved in tight containers protected from light.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Arsenic trioxide concentrate for solution for infusion is a clear and colourless solution. Each 10 mL contains 10 mg arsenic trioxide as the active substance. It is a sterile solution for single use and contains no antimicrobial preservative. The pH of arsenic trioxide concentrate is between 6.0-8.0. Arsenic trioxide concentrate is diluted before use.

The finished product has been developed to be a generic equivalent to the reference medicinal product Trisenox 1 mg/mL concentrate for solution for infusion. Consequently, the objective was to prepare a parenteral formulation being essentially similar to the reference medicinal product.

The active substance is sparingly soluble in cold water and dissolves readily in alkaline solutions to give arsenites. Arsenic trioxide is compatible with the excipients sodium hydroxide, hydrochloric acid, nitrogen gas and water for injections.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The commercial formulation of Trisenox utilises 1.2 mg/mL of sodium hydroxide for solubilisation and hydrochloric acid for pH adjustment. Given the stated use of sodium hydroxide in the formulation, the formulations of the reference and generic medicinal product are equivalent in this respect. The reference medicinal product is adjusted to a pH range of 7.0 to 9.0. These minor differences in formulation between the reference and the generic medicinal product would have no effect on the bioequivalence of the two intravenous injections.

The finished product is manufactured for the market as an aqueous, sterile injection intended for single use only. The general manufacturing methodology for producing aqueous, sterile injectable involves blending, filling the solution into vials, sealing of the vials, terminal steam sterilization, visual inspection and labelling and packaging. The manufacturing process was developed using Good Manufacturing Practice and In House Standard Operating Procedures to produce a sterile solution in a glass, rubber capped vial. The manufacturing process has been validated. Autoclave studies were carried out and the formulation was found to be stable when steam sterilised. The sterilisation method complies with the British Pharmacopeia (BP) sterility methods.

The primary packaging is comprised of a type I glass vial, chlorobutyl rubber stopper and seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. To ensure compatibility of the stopper with the product, an extractables and leachables study as well as container integrity was conducted. No concerns were identified.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: dissolution of the active substance and pH adjustment, filtration, filling the solution into vials, sealing of the vials, terminal steam sterilization, visual inspection and labelling and packaging. The process is considered to be a non-standard manufacturing process.

The manufacturer of the finished product has a large portfolio of sterile injectable drugs that have been manufactured by the company for over two decades. The experience and the know-how gained have been used during the development of manufacturing process for this product.

Major steps of the manufacturing process have been validated in three consecutive production scale batches by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), visible particles (Ph. Eur.), identification (Ph. Eur.), pH of solution (Ph. Eur.), related substances (HPLC), assay (titration), extractable volume (Ph. Eur.), sub-visible particles (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and sterility (Ph. Eur.).

The in-use specification for the finished product after dilution include appropriate tests: appearance (visual), clarity of solution (visual), visible particles (Ph. Eur.), pH of the solution (Ph. Eur.), related substances (HPLC), sub-visible particles (Ph. Eur.) and assay (HPLC).

There is no Ph. Eur. monograph for arsenic trioxide injection on which to base the specifications for arsenic trioxide concentrate. There is a monograph *Arsenii trioxidum ad praeparationes homoeopathicas* in Ph. Eur. on which the raw material specification is partially based. Arsenic trioxide 1mg/ml concentrate complies with the requirements stated under the general Ph. Eur. monograph for parenteral preparations.

Potential impurities and degradation products are controlled during the synthesis of the active substance. For the major impurity the finished product specification provides a limit and limits for unidentified impurities and total impurities are also provided.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data were provided for 4 batches. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is considered satisfactory.

The risk assessment into the presence of nitrosamines has shown that there is no significant risk of *N*-nitrosamine impurities being present within the finished product. As such, a test for these impurities is not required.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 36 months under long term conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were stored upside-down, so that product is in contact with stoppers and leakages can be detected.

Samples were tested for appearance, assay, pH, related substances, extractable volume, sub-visible particles, bacterial endotoxins and sterility. The analytical procedures used are stability indicating.

Under long term and accelerated stability conditions, the results were all within the proposed specification. No trends were noted.

Stability data for the next three batches indicate there is no change to the stability of product due to the change in batch size. Results for vials stored under accelerated conditions for 6 months indicate the product is stable. Available results for vials stored at 30°C (1 batch for 18 months and two for 24 months) indicate the product will continue to be stable up to 36 months when stored below 30°C

In addition, 2 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Two storage conditions were used – dark control and exposed to light test. The differences in results between the dark control samples and the exposed test samples were within the acceptance limits. Thus, it is confirmed that the finished product is not light sensitive when stored in the container packaging.

A compatibility study which also addressed in-use stability has been completed. Two batches were diluted in both 100 mL and 250 mL of 5% glucose, and also in 100mL and 250mL of 0.9% NaCl. The diluted solutions were stored at 2-8°C and at 30°C and tested up to 72 hours. All test results were within specification. Thus, it is confirmed that the finished product when diluted in 100 mL or 250 mL of glucose or saline intravenous solution is chemically stable for up to 72 hours when stored at 2-8°C or 30°C.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

After dilution in intravenous solutions, the finished product is chemically and physically stable for 24 hours at 15°C-30°C and 48 hours when refrigerated (2°C-8°C). 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°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To provide the validation data of the ICP-OES method to test metallic arsenic in the active substance together with the next variation.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The Applicant performed the Phase I of the ERA according to the ERA guideline *(EMEA/CHMP/SWP/4447/00 corr 2)*. The calculated $PEC_{surfacewater}$ is below the threshold value of 0.01 µg/L stated in the ERA guideline, therefore a Phase II assessment is not required. As PBT and vPvB criteria do not apply to inorganic substances, log K_{ow} determination for Arsenic trioxide medac is not required, either. Considering the above-presented data, Arsenic trioxide medac is unlikely to represent a risk to the environment following its prescribed usage in patients.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview provides a sufficient outline on the available literature concerning the non-clinical pharmacology, pharmacokinetics and toxicology of arsenic trioxide which is considered adequate.
Cross-references to the scientific literature proposed by the Applicant have been included in each part of the Non-Clinical Overview, as requested by the CHMP.

2.3.4. Conclusion on the non-clinical aspects

The CHMP is of the opinion that the applicant has justified the absence of non-clinical studies based on the literature review and the claim that Arsenic trioxide medac is a generic of the reference product Trisenox. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Arsenic trioxide medac in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of arsenic trioxide based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) is relevant.

Exemption

This is a generic application for a medicinal product supplied as a concentrate for solution for infusion in glass vials for single use. According to the Appendix II of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**): "Bioequivalence studies are generally not required if the test product is to be administered as aqueous intravenous solution containing the same active substance as the currently approved product". No bioequivalence study was conducted, and none is required, since the product is to be administered as an aqueous solution for injection for intravenous administration containing the same active substance in the same concentrations, the same pharmaceutical form and route of administration as the currently authorised reference medicinal product. In addition, Arsenic trioxide medac contains the same excipients as the reference medicinal product and the excipients are not known to interact with the drug substance or to otherwise affect the disposition of the drug substance.

Therefore, for the current generic application, the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence, which is accepted by the CHMP.

2.4.2. Pharmacokinetics

The product is to be administered as an intravenous infusion containing the same active substance and the same excipients as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence.

The essential similarity with the reference medicinal product is based only on pharmaceutical equivalence.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

No bioequivalence study was submitted to support the application and this is acceptable as being in accordance with the Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Arsenic trioxide medac is considered essentially similar to Trisenox Teva B.V.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Arsenic trioxide medac and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	- None
Important potential risks	- Carcinogenicity
Missing information	- Long-term safety

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Carcinogenicity	Routine risk minimisation measures: SmPC sections 4.4 and 5.3 PL section 2 SmPC section 4.4: Monitoring for the development of second primary malignancies is recommended. Prescription only Arsenic trioxide must be administered under the supervision of a physician who is experienced in the management of acute leukaemias. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety	Routine risk minimisation measures: Prescription only Arsenic trioxide must be administered under the supervision of a physician who is experienced in the management of acute leukaemias. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the

list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of Arsenic trioxide medac 1 mg/ml concentrate for solution for infusion. The indication of the reference product Trisenox is as follows:

TRISENOX is indicated for induction of remission, and consolidation in adult patients with:

• Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA)

• Relapsed/refractory acute promyelocytic leukaemia (APL) (previous treatment should have included a retinoid and chemotherapy)

characterised by the presence of the t(15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Arsenic trioxide medac is favourable in the following indication:

"Arsenic trioxide medac is indicated for induction of remission, and consolidation in adult patients with:

- Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA)
- Relapsed/refractory APL (previous treatment should have included a retinoid and chemotherapy)

characterised by the presence of the t(15;17) translocation and/or the presence of the promyelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined".

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Arsenic trioxide medac is not similar to Dacogen, Mylotrag, Vyxeos, Rydapt, Xospata, and Daurismo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.