19 September 2019
EMA/CHMP/580349/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Arsenic trioxide Accord

International non-proprietary name: arsenic trioxide

Procedure No. EMEA/H/C/005175/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Administrative information

Name of the medicinal product:	Arsenic trioxide Accord
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6a Planta 08039 Barcelona SPAIN
Active substance:	ARSENIC TRIOXIDE
International non-proprietary name/Common name:	arsenic trioxide
Pharmaco-therapeutic group (ATC Code):	antineoplastic agents, other antineoplastic agents (L01XX27)
Therapeutic indication(s):	Arsenic trioxide 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 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.
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):	1 vial, 5 vials and 10 vials

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List of abbreviations

Ph. Eur. - European Pharmacopoeia

PFS - Pre-filled syringe

WFI - Water for Injection

CoA - Certificates of analysis

NLT – Not less than

NMT – Not more than

IPC - In Process Control

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-OES - Inductively coupled plasma - optical emission spectrometry

LAL - Limulus amebocyte lysate

PDEs - Permissible daily exposure

OOS – Out of Specification

SS - Stainless Steel

LOD – Limit of detection

LOQ – Limit of quantitation

API – active pharmaceutical ingredient

DMF – Drug master File

EC - European Commission

ASMF – Active Substance Master File

HPLC – High-performance liquid chromatography

NfG – Note for Guidance

RA – Risk Assessment

QP – Qualified Person

RMP – Risk management Plan

RH - Relative Humidity

USP - The United States Pharmacopeia

XRD – X-Ray diffraction

NaOH – sodium hydroxide

AF- Application Form

PI – Product Information

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 26 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Arsenic trioxide Accord, 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 18 October 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 in the Union 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 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 103/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 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 data 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 at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

The application was received by the EMA on	26 November 2018
The procedure started on	28 December 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 February 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 May 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	1 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	4 September 2019

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 Accord on	19 September 2019

2. Scientific discussion

2.1. Introduction

This application is for marketing authorization of Arsenic trioxide Accord 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 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.

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 as active substance.

Other ingredients are: sodium hydroxide, concentrated hydrochloric acid (for pH adjustment) and water for injections.

The product is available in Type I transparent colourless glass vial sealed with a silicon-oil free, elastomer type, grey bromobutyl rubber stopper and aluminium seal with a plastic flip off cap, containing 10 ml of concentrate, 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:

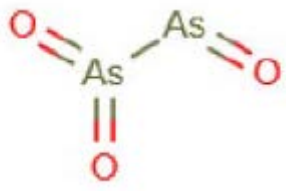

Figure 1: Active substance structure

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 (NaOH 1 M), 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 specification.

Critical steps identified are well controlled during production. No In Process Controls or specifications of intermediate products are established. 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 bottle with blue closure as a primary container which complies with the EC regulation 10/2011 as amended.

Specification

The active substance specification from the finished product manufacturer includes tests for appearance (visual), solubility (Ph.Eur.), identification (chemical, HPLC), appearance of solution (Ph. Eur.), pH of solution (Ph. Eur.), assay (titration), metallic arsenic (gravimetric), As2O5 content (HPLC) , loss on drying

(Ph. Eur.), metallic impurities (ICP-OES) , iron content (ICP-OES), endotoxins (LAL test), and microbial analysis (Ph. Eur.).

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 of 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 (25 ºC / 60% RH and 30ºC / 75% HR)) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The tests and analytical methods used were the same as for release and were 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

The finished product arsenic trioxide 1 mg/ml concentrate for solution for infusion is a clear and colourless aqueous solution. The solution is sterile, non-pyrogenic and essentially free of particles.

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 practically insoluble to sparingly soluble in water. It dissolves in solutions of alkali hydroxides (1M NaOH).

It is considered that the qualitative and quantitative composition of the generic medicinal product is similar to that of the reference medicinal product. 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.

For the development of the formulation the following representative points (quality target product profile) were taken into consideration: qualitative / quantitative composition should be similar to reference medicinal product; sterility must be met during release, shelf life and in-use period; specific (compendial) requirements for parenteral preparations should be ensured; establishing a manufacturing technology so as to ensure continuity in solution preparation, by optimal and reliable production parameters; sterilization of the finished product by filtration through a bacteria-retentive filter, followed by aseptic vial filling in sterile primary packaging should be used; and finally, sterilization of filled and sealed vials. The finished product obtained as a result of pharmaceutical development has been assessed with regard to its physico-chemical parameters and stability. The developed product is regarded to be comparable to the reference medicinal product.

In relation to the manufacturing process development, different manufacturing steps (bulk solution preparation, filtration, vial filling, and terminal sterilization) were assessed carefully and a gentle procedure ensuring the production of a finished product of reliable quality has been chosen.

The primary packaging is Type I transparent colourless glass vial sealed with a silicon-oil free, elastomer type, grey rubber stopper and aluminium seal with a plastic flip off cap. The material complies 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.

Manufacture of the product and process controls

The finished product is a sterile product manufactured by sterilization of filled vials. The manufacturing process consists of 5 main steps: weighing of the incoming materials, preparation of bulk solution, pre-filtration, vial filling (the step includes 2nd filtration and filling), and terminal sterilization.

Major steps of the manufacturing process have been validated by a number of studies in three commercial scale batches. 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, identification (HPLC, chemical), pH (Ph. Eur.), extractable volume (Ph. Eur.), assay (HPLC), particulate contamination (Ph. Eur.), related substances (HPLC), sterility (Ph. Eur.), and bacterial endotoxins (Ph. Eur.).

Impurities may well be present in the finished product, but these compounds are likely to originate from active substance synthesis and are adequately controlled in the active substance.

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. From the assessment of the finished product components, the daily contribution to the total mass of elemental impurities that may be present in the finished product was calculated. Calculation option 2b was used based on the maximum expected concentration of elemental impurities which may be present in the individual components also considering the actual maximum daily intake of the finished product. This calculation revealed that the total daily intake of Class 1 and Class 2A as well as Class 3 elements is far below the 30% control threshold for parenteral permissible daily exposure (PDEs). Actual testing revealed levels considerably lower than those predicted using calculation Option 2b. Thus, no additional controls are to be imparted in the finished product specification.

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 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 production scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

No significant observations were recognized under long term stability conditions. All results of testing at accelerated conditions met the specifications established for shelf life and confirm a satisfying stability of the final finished product at this storage condition.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data demonstrates that during the study neither the physical nor the chemical properties of the finished product exposed to light show significant changes. Therefore, it can be concluded that the finished product is not sensitive to light.

Identically with the innovator product, Arsenic Trioxide Accord must be diluted with 100 to 250 ml of glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection immediately after withdrawal from the vial. The applicant performed an in-use stability study on the finished product. The results were comparable to those from the reference product and clearly demonstrate that stability of the finished product during the shelf life when diluted in 0.9 % sodium chloride or 50 mg/mL (5 %) glucose solution when stored up to 48 hours at 2-8 °C, or up to 24 hours at room temperature.

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

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C and 48 hours at 2°C to 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.

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

Not applicable

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

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Arsenic trioxide Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all arsenic trioxide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the CHMP agreed that no further non-clinical studies are required.

The impurity profile of applicant's Arsenic trioxide is comparable to that of Trisenox. Thus, additional toxicology studies to qualify the impurity profile of the drug product are not required.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

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 Accord 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 Accord in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The clinical overview on the clinical pharmacology, efficacy and safety has been provided. The Clinical sections of the SmPC of Arsenic trioxide Accord are in accordance with the reference product Trisenox 1 mg/ml concentrate for solution for infusion, first authorised within the EU on the 05-03-2002 under registration number EU/1/02/204/001.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product. The CHMP considers that the clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Exemption

No bioequivalence study was submitted to support the application. According to Appendix II to 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 an aqueous intravenous solution containing the same active substance as the currently approved product. This is the case here. Both products, generic product Arsenic trioxide Accord and the reference product Trisenox, contain 1.0 mg of the same active substance, arsenic trioxide, and the same excipients. Therefore, it is concluded that there is no difference between the Arsenic trioxide Accord and Trisenox. A bioequivalence study is not required.

2.4.2. Pharmacodynamics

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

2.4.3. Post marketing experience

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

2.4.4. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

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

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

2.4.5. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Arsenic trioxide Accord 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

The applicant identified the following safety concerns in the updated RMP (version 1.2, dated

06.08.2019).

Safety concerns

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

Pharmacovigilance plan

There is no on-going and planned studies in the post-authorisation pharmacovigilance plan proposed in the RMP of Arsenic trioxide Accord.

However, there is one PASS study mentioned in the EPAR of the reference product Trisenox:

A post-authorization long term safety cohort study in acute promyelocytic leukaemia (APL) patients treated with Trisenox (Category 3).

Objective: To assess the long-term safety of ATRA+ATO in newly diagnosed low to intermediate risk APL patients in a real-world clinical practice setting.

Status: planned

Safety concerns addressed: long-term safety and carcinogenicity

Date for submission of interim or final reports:

Interim report 1: 4Q 2019

Interim report 2: 4Q 2021

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Carcinogenicity	Routine risk minimisation measures: SmPC section: 4.4 Special warnings and precautions for use *5.3* Preclinical safety data Labelling Section: 7. Other special warnings: Cytotoxic: handle with caution. Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: No additional pharmacovigilance activities are planned.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	Routine risk minimisation measures: Prescription only medicine 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 1.2 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Trisenox (for text content) and Solifenacin succinat Accord 5 mg and 10 mg film-coated tablets (for the layout). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Arsenic trioxide Accord 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 103/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 that the benefit-risk balance of Arsenic trioxide Accord is favourable in the following indication:

Arsenic trioxide 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 103/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 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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

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.