30 January 2020
EMA/CHMP/638190/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Arsenic trioxide Mylan

International non-proprietary name: arsenic trioxide

Procedure No. EMEA/H/C/005235/0000

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

Table of contents

List of abbreviations

ASMF Active Substance Master File = Drug Master File

CHMP - the Committee for Medicinal Products for Human Use

CQA Critical Quality Attribute

EC European Commission

EMA - European Medicines Agency

ERA - Environmental Risk Assessment

GLP - Good Laboratory Practice

HPLC High performance liquid chromatography

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

IPC In-process control

ICP-MS Inductively coupled plasma-mass spectrometry

ICP-OES Inductively coupled plasma-optical emission spectrometry

IR Infrared

kg - Kilogram

Log K_{ow} - n-octanol/water partition coefficient

LoQ - List of Questions

mg - Miligram

mL - Millilitre

PDE Permitted Daily Exposure

Ph. Eur. European Pharmacopoeia

QTPP Quality target product profile

SmPC - Summary of Product Characteristics

TAMC Total Aerobic Microbial Count

TYMC Total Combined Yeasts/Moulds Count

USP United States Pharmacopoeia

UV Ultraviolet

XRD X-Ray Diffraction

APL - Promyelocytic lLukaemia

AML - Acute Myelocytic Leukaemia

RAR-alpha - Retinoic-Acid-Receptor-alpha gene

ATRA - all-trans-retinoic acid

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

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
AF- Application Form
PI – Product Information

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 7 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Arsenic trioxide Mylan, 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 in 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 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.

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 at 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	7 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	01 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 October 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	18 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 a list of outstanding issues to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	07 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 January 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 Mylan on	30 January 2020
The CHMP adopted a report on similarity of Arsenic Trioxide Mylan with Dacogen, Mylotrag, Vyxeos, rydapt amd Xospata	30 January 2020

2. Scientific discussion

2.1. Introduction

This application is for marketing authorisation of Arsenic trioxide Mylan 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

Hydrochloric acid (as pH adjuster)

Water for injections

The finished product is available in Type I clear glass vial closed with bromobutyl stoppers and with aluminium flip-off caps as described in section 6.5 of the SmPC.

2.2.2. Active substance

Arsenic trioxide is not described in the European Pharmacopoeia, pharmacopoeias of the Member States or USP. The documentation on the active substance is presented using an Active Substance Master File (ASMF) procedure.

The ASMF has been assessed as part of an EU ASMF work sharing procedure as a daughter procedure. The ASMF is registered with the number EU/ASMF/00235/0001. The information provided in the Applicant's and Restricted parts of the ASMF are considered sufficient to support the marketing authorisation application for the finished product.

General information

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

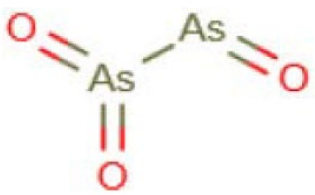

Figure 1: active substance structure

The chemical structure and solid-state properties of arsenic trioxide were elucidated by a combination of Crystallography (XRD), Thermogravimetric analysis, Hygroscopy and IR spectroscopy.

Arsenic trioxide is a white to an off-white non-hygroscopic powder, practically insoluble to sparingly soluble in water, soluble in solutions of alkali hydroxides (NaOH 1M). Practically insoluble in ethanol, chloroform and ethyl ether. It does not contain any sterocentres.

Arsenic trioxide exhibits polymorphism. Given that the active substance is to be formulated into a concentrate for solution for infusion, the absence of controls for polymorphism is considered acceptable.

Manufacture, characterisation and process controls

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

Arsenic trioxide is synthesized from the starting material elementary arsenic.

Adequate in-process controls are applied during the synthesis. 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 new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. A discussion on genotoxic impurities was not provided, however this was considered acceptable, since the active substance itself is genotoxic and the impurities are unlikely to pose a significant additional genotoxic risk.

Arsenic trioxide is packed in high-density polyethylene bottle with a plastic closure as a primary container. Bottles with integrated tamper evidence ring are placed in a sealed polyethylene bag used as secondary packaging. The packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, solubility (Ph. Eur.), identity (chemical, HPLC), appearance of solution (Ph. Eur.), pH of solution (Ph. Eur.), assay (titration), metallic arsenic content (gravimetric), Arsenic pentoxide (As_2O_5) content (HPLC), loss on drying (Ph Eur), metallic impurities (ICP-OES), iron content (ICP-OES), bacterial endotoxins (Ph. Eur.) and microbiological analysis (Ph. Eur.).

Impurities limits have been justified and appropriate specifications have been set. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

With regards to elemental impurities, no other metals are intentionally added. As the active substance is to be used in parenteral formulation, elemental impurities are controlled in the active substance specification, in line with the ICH Q3D guideline. Other potential impurities from arsenic powder are not controlled in the active substance but are controlled in the starting material specification.

Batch analysis data (three full scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data was provided from three production scale batches of active substance from the proposed manufacturer stored in the intended commercial packaging for up to 24 months at long-term (25±2°C 60±5% RH), intermediate (30ºC / 75% RH) storage conditions and for up to 6 months at accelerated conditions (40±2°C 75±5%) RH according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Forced degradation study (stress testing) has been performed and confirmed that the HPLC method is stability indicating.

Photostability testing in line with the ICH Q1B guideline was not presented, however the proposed storage conditions to protect the substance from light are supported by stress testing results where photolytic degradation was confirmed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The proposed retest period and storage conditions are justified.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a concentrate for solution for infusion containing 1 mg/mL arsenic trioxide as active substance. The concentrate contains sodium hydroxide, hydrochloric acid, water for injection. Nitrogen is used as processing agent.

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 goal of pharmaceutical development was to develop a generic formulation of arsenic trioxide which is bioequivalent to the reference product Trisenox 1 mg/ml, which was approved by EMA in 2002 throughout the European Union. The finished product is preservative free and has been developed as a sterile, non-pyrogenic, clear solution.

Based on information including composition, ingredients, container closure and product development a quality target product profile (QTPP) was established.

Based on the QTPP process parameters were assessed for criticality with respect to the critical quality attributes (CQA) for the formulation and process development of the finished product. A comparison of the formulation in development with the formulation of reference product Trisenox was completed.

The manufacturing process development is discussed in detail. The bulk solution is filled into primary packaging and followed by terminal sterilization. The time and temperature conditions for the terminal sterilisation is ≥121°C for >15 minutes in line with Reference Cycle as per Ph. Eur. 5.1.1.

The critical steps and in-process control were validated during the manufacture of three validation batches of industrial scale.

The primary packaging is Type I clear glass vial (Ph. Eur.) closed with bromobutyl stoppers and with aluminium flip-off caps. 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.

Manufacture of the product and process controls

- The manufacturing process consists of six main steps: Step I Bulk solution preparation

- Step II Pre-filtration into a storage vessel
- Step III Vial filling process
- Step IV Terminal sterilization of the filled vials in an autoclave
- Step V Visual inspection of the vials
- Step VI Labeling and secondary packaging

The process is considered to be a standard manufacturing process.

The critical steps have been defined. These critical steps are monitored by respective in-process controls.

Major steps of the manufacturing process have been validated by a number of studies. The process validation was carried out on 3 consecutive production 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 & pharmaceutical form.

Product specification

The finished product release specifications shown include appropriate tests for this kind of dosage form; appearance, identification (HPLC, chem), pH (Ph. Eur.), extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), visible particulates (Ph. Eur.), related substances (HPLC), assay (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The finished product is released on the based on the above release specifications, through traditional final product release testing. The limits for impurities are in accordance with ICH Q3B (R2).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. 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. The information on the control of elemental impurities is satisfactory.

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 three 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 three batches of finished product stored for up to 12 months at long-term (25°C±2°C/60%±5% RH, 30°C±2°C/65%±5% RH) and at 2-8°C, and stability data up to 6 months at accelerated (40°C±2°C/ 75%±5% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for in line with the shelf life specifications. The analytical procedures used are stability indicating. All results comply with the shelf-life specifications.

A photostability study has been conducted according to conditions of ICH Q1B. The finished product exposed to the conditions in clear glass vials and exposed when packaged in its secondary packaging, remained stable and there are no significant differences to the dark control sample.

The results of an in-use stability study of the finished product diluted with 0.9% sodium chloride and 5% glucose infusion media has confirmed stability up to 48 hours stored at 2-8°C and up to 24 hours stored at 15°C-25°C. This information is included in section 6.3 of the SmPC.

Based on available stability data, the proposed shelf-life of shelf-life of 24 stored in the original container with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress and to investigate the risk of presence of nitrosamine in their medicinal products, the CHMP recommends the following points for investigation:

- It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities in Arsenic trioxide Mylan is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

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 Mylan manufactured by Mylan Ireland Limited 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. 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 Mylan 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 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 Mylan 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. 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

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 Mylan 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 Mylan 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

Table SVIII.1: Summary of safety concerns

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

Pharmacovigilance plan

Safety concern	Pharmacovigilance activities
Carcinogenicity	Routine pharmacovigilance activities
Long-term safety	Routine pharmacovigilance activities

Risk minimisation measures

Safety concern	Risk minimisation measures
Carcinogenicity	Routine risk minimization measures

Safety concern	Risk minimisation measures
Long-term safety	Routine risk minimization measures

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 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 two bridging reports making reference to Trisenox and Tranexamic Acid Mylan. The bridging reports submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Arsenic trioxide Mylan 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 Mylan is favourable in the following indication:

"Arsenic trioxide Mylan 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".

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.