

Arsenic trioxide

Date: 2019-04-10

Revision date: 2026-03-04

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EU Risk Management Plan for Arsenic trioxide medac 1 mg/ml concentrate for solution for infusion (arsenic trioxide)

RMP version to be assessed as part of this application:

RMP Version number:	1.0
Data lock point for this RMP:	15/02/2026
Date of RMP finalisation:	04/03/2026
Rationale for submitting an updated RMP:	Adaption to reference product Trisenox
Summary of significant changes in this RMP:	Alignment of the list of safety concerns to the reference medicinal product: Update of Part II SVIII, Part V.2 and V.3 and Part VI

Other RMP versions under evaluation:

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

Version number:	0.2
Approved with procedure:	EMA/H/C/0005218/0000
Date of approval (opinion date):	23/07/2020

EU-/UK-QPPV name: Dr. med. Barbara Jogereit

EU-/UK QPPV signature/oversight declaration:

The content of this RMP has been reviewed and approved by the MAH's QPPV. The electronic signature is available on file.

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ABBREVIATIONS:

ADR	Adverse Drug Reaction
APL	Acute Promyelocytic Leukaemia
ATC	Anatomical Therapeutic Chemical Classification System
ATRA	All-Trans-Retinoic Acid
DNA	Deoxyribonucleic Acid
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
INN	International Nonproprietary Name
PML/RAR-alpha	Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha
PSMF	Pharmacovigilance System Master File
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Arsenic trioxide
Pharmacotherapeutic group(s) [ATC Code]	Other antineoplastic agents [L01XX27]
Marketing Authorisation Applicant	medac Gesellschaft für klinische Spezialpräparate mbH Theaterstraße 6 22880 Wedel / Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Arsenic trioxide medac
Marketing authorisation procedure	Centralised procedure (EMEA/H/C/005218/CP)
Brief description of the product	<i>Chemical class:</i> Antineoplastic and immunomodulating agents - other antineoplastic agents
	<i>Summary of mode of action:</i> The mechanism of action of Arsenic trioxide medac is not completely understood. Arsenic trioxide causes morphological changes and deoxyribonucleic acid (DNA) fragmentation characteristic of apoptosis in NB4 human promyelocytic leukaemia cells <i>in vitro</i> . Arsenic trioxide also causes damage or degradation of the fusion protein pro-myelocytic leukaemia/retinoic-acid-receptor-alpha (PML/RAR-alpha).
	<i>Important information about its composition:</i> None
Hyperlink to the Product Information	eCTD: 1.3.1
Indication(s) in the EEA	<i>Current:</i> Arsenic trioxide medac is indicated for induction of remission, and consolidation in adult patients with: <ul style="list-style-type: none">– Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, $\leq 10 \times 10^3 /\mu\text{l}$) 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 PML/RAR-alpha gene. The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.

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	<p><i>Proposed:</i> Not applicable</p>
Dosage in the EEA	<p><i>Current:</i> <u>Newly diagnosed low-to-intermediate risk APL:</u> <i>Induction treatment schedule:</i> Arsenic trioxide medac must be administered intravenously at a dose of 0.15 mg/kg/day, given daily until complete remission is achieved. If complete remission has not occurred by day 60, dosing must be discontinued. <i>Consolidation schedule:</i> Arsenic trioxide medac must be administered intravenously at a dose of 0.15 mg/kg/day, 5 days per week. Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles. <u>Relapsed/refractory APL:</u> <i>Induction treatment schedule:</i> Arsenic trioxide medac must be administered intravenously at a fixed dose of 0.15 mg/kg/day given daily until complete remission is achieved (less than 5% blasts present in cellular bone marrow with no evidence of leukaemic cells). If complete remission has not occurred by day 50, dosing must be discontinued. <i>Consolidation schedule:</i> Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. Arsenic trioxide medac is to be administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks. <i>Method of administration:</i> Arsenic trioxide medac must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed.</p> <p><i>Proposed:</i> Not applicable</p>
Pharmaceutical form(s) and strengths	<p><i>Current:</i> Concentrate for solution for infusion. Sterile, clear, colourless, aqueous solution. 1 mL of Arsenic trioxide medac contains 1 mg of arsenic trioxide.</p> <p><i>Proposed:</i> Not applicable.</p>

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Is/will the product be subject to additional monitoring in the EU?	No
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PART II: SAFETY SPECIFICATION

MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

MODULE SIII - CLINICAL TRIAL EXPOSURE

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

MODULE SV - POST-AUTHORISATION EXPERIENCE

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

Arsenic trioxide medac is a generic product and therefore this section is not applicable.

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MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

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

The list of safety concerns has been aligned to those of the reference medicinal product Trisenox following the update of its RMP to version 3.0 in which the important potential risk 'Carcinogenicity' and the missing information topic 'Long-term safety' were removed following completion of a PASS for Trisenox. The remaining safety concern of Trisenox, i.e. the important potential risk 'Medication errors caused by confusion between the different concentrations' is not applicable for Arsenic trioxide medac as it is only provided in one concentration.

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PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The company collects and monitors all spontaneously reported adverse events and commits to a detailed assessment of each report as part of routine pharmacovigilance activities. All events reported to the company or published in the literature will be periodically assessed for trends and the product information will be kept up to date in accordance with the relevant EU Directives.

The company's pharmacovigilance system including routine pharmacovigilance activities is described in its pharmacovigilance system master file (PSMF) and summarised in eCTD Module 1.8.1.

Routine pharmacovigilance activities beyond adverse drug reactions (ADR) reporting and signal detection:

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities: None

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

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PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There were no post-authorisation efficacy studies imposed for medac GmbH, therefore, this section is not required.

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PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 ROUTINE RISK MINIMISATION MEASURES

Not applicable since no safety concerns are included in the list of safety concerns (Part II, Module SVIII).

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Not applicable

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Not applicable

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Arsenic trioxide medac (arsenic trioxide)

This is a summary of the risk management plan (RMP) for Arsenic trioxide medac. The RMP details important risks of Arsenic trioxide medac, how these risks can be minimised, and how more information will be obtained about Arsenic trioxide medac's risks and uncertainties (missing information).

Arsenic trioxide medac's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Arsenic trioxide medac should be used.

This summary of the RMP for Arsenic trioxide medac should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Arsenic trioxide medac's RMP.

I. The medicine and what it is used for

Arsenic trioxide medac is authorised for treatment of APL in adult patients (see SmPC for the full indication). It contains arsenic trioxide as the active substance and it is given intravenously.

Further information about the evaluation of Arsenic trioxide medac's benefits can be found in Arsenic trioxide medac's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage [<link to the EPAR summary landing page on the EMA webpage>](#).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Arsenic trioxide medac, together with measures to minimise such risks and the proposed studies for learning more about Arsenic trioxide medac's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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II.A List of important risks and missing information

Important risks of Arsenic trioxide medac are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Arsenic trioxide medac. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	- None
Important potential risks	- None
Missing information	- None

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II.B Summary of important risks

No risks are classified as important, therefore this section is not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Arsenic trioxide medac.

II.C.2 Other studies in the post-authorisation development plan

There are no studies required for Arsenic trioxide medac.

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PART VII: ANNEXES

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ANNEX 1 - EUDRAVIGILANCE INTERFACE

Not applicable

ANNEX 2 - TABULATED SUMMARY OF PLANNED, ON-GOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Not applicable

ANNEX 3 - PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Not applicable

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 5 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable

ANNEX 7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

None

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ANNEX 8 - SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date Procedure	Change
0.1	Marketing authorisation application procedure	
0.2	17/09/2020 EMA/H/C/0005218/0000	Alignment of the list of safety concerns to the reference medicinal product Update of Part V Modules V.1 and V.3 Update of Part VI
1.0	Submitted within a variation to adapt the safety concerns to the reference medicinal product product Trisenox	<u>Safety concerns</u> Alignment of the list of safety concerns to the reference medicinal product: Important potential risk removed: - Carcinogenicity Missing information removed: - Long-term safety