EU RISK MANAGEMENT PLAN

TRISENOX (arsenic trioxide)

RMP version to be assessed as part of this application	
RMP version number	3.0
Data lock point for this RMP	30 April 2025
Date of final sign off	13 June 2025
Rationale for submitting an updated RMP	Submission of Final Study Report for Post-Authorisation Long-Term Retrospective Safety Cohort Study of Arsenic Trioxide in First Line Low- to Intermediate-Risk Acute Promyelocytic Leukaemia and removal of “Carcinogenicity” and “Long-term safety” from the list of safety concerns in line with final study report results.

QPPV Details	
QPPV name:	Iva Novak
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy. The signature is available on file.

Table 1: Summary of Significant Changes in This RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Product(s) overview	2.3 (27 May 2019)	Not applicable
Part II - Module SI Epidemiology of the indication(s) and target population(s)	2.3 (27 May 2019)	Not applicable
Part II - Module SII Non-clinical part of the safety specification	2.3 (27 May 2019)	Not applicable
Part II - Module SIII Clinical trial exposure	2.3 (27 May 2019)	Not applicable
Part II - Module SIV Populations not studied in clinical trials	2.3 (27 May 2019)	Not applicable
Part II - Module SV Post-authorisation experience	2.3 (27 May 2019)	The section has been updated to include the most recent patient exposure data.
Part II - Module SVI Additional EU requirements for the safety specification	2.3 (27 May 2019)	Not applicable
Part II - Module SVII Identified and potential risks	2.3 (27 May 2019)	Section revised to remove important potential risk "Carcinogenicity" and missing information "Long-term safety" from the list of safety concerns.
Part II - Module SVIII Summary of the safety concerns	2.3 (27 May 2019)	Section revised to remove important potential risk "Carcinogenicity" and missing information "Long-term safety" from the list of safety concerns.
Part III Pharmacovigilance plan (including post-authorisation safety studies)	2.3 (27 May 2019)	The section has been updated to reflect changes in the pharmacovigilance plan.
Part IV Plans for post-authorisation efficacy studies	2.3 (27 May 2019)	Not applicable

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	2.3 (27 May 2019)	The section has been updated to reflect changes in the pharmacovigilance plan and removal of important potential risk “Carcinogenicity” and missing information “Long-term safety” from the list of safety concerns. .
Part VI Summary of the risk management plan	2.3 (27 May 2019)	The section has been updated to reflect changes in the pharmacovigilance plan and removal of important potential risk “Carcinogenicity” and missing information “Long-term safety” from the list of safety concerns.
Part VII Annexes	2.3 (27 May 2019)	Annex 3 and Annex 4 are no longer applicable due to PASS finalisation. Annex 8 was updated to reflect changes in the pharmacovigilance plan and removal of important potential risk “Carcinogenicity” and missing information “Long-term safety” from the list of safety concerns.

Details of the currently approved RMP	
Version number	2.3
Approved with procedure	EMEA/H/C/000388
Date of approval (opinion date)	27 May 2019

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
$As(OH)_3$	Arsenous acid
As_2O_3	Arsenic trioxide
AS3MT	Arsenic methyltransferase
AsH_3	Hydride of trivalent arsenic
AsIII	Arsenite
AST	Aspartate aminotransferase
AsV	Arsenate
ATC	Anatomical Therapeutic Chemical
ATO	Arsenic trioxide
ATRA	All-trans-retinoic acid
AV	Arteriovenous
BW	Body Weight
CHMP	Committee of Human Medicinal Products
CI	Confidence Interval
CIR	Cumulative Incidence of Relapse
CKD	Chronic Kidney Disease
CNS	Central Nervous System
DFS	Disease-Free Survival
e.g.	example given
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus

HLT	High Level Term
i.e.	Id est (engl.: that means)
i.v.	Intravenous
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
IU	International Unit
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Monomethylarsonic acid
MMAV	Monomethylarsonate
mRNA	Messenger RNA
MTD	Maximum Tolerated Dose
NB4	A maturation inducible cell line with t(15;17)
NEC	Not Elsewhere Classified
OS	Overall Survival
PASS	Post-Authorisation Safety Study
Ph. Eur.	European Pharmacopoiea
PL	Package Leaflet
PML	Promyelocytic leukaemia protein
PSUR	Periodic Safety Update Report
s.c.	Subcutaneous
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SP	Safety Population (In Clinical Trials)
SPC, SmPC	Summary Of Product Characteristics
TdP	Torsade de Pointes
TEAE	Treatment-Emergent Adverse Event
tMDS	Treatment-related myelodysplastic syndrome
UK	United Kingdom
ULN	Upper Limit of Normal
US(A)	United States (of America)
WBC	White Blood Cell
WHO	World Health Organisation

Part I: Product(s) Overview

Table 2: Product Overview

Active substance(s) (INN or common name)	**Arsenic trioxide**
Pharmacotherapeutic group(s) (ATC Code)	Other antineoplastic agents (L01XX27)
Marketing Authorisation Holder	TEVA B.V. Swensweg 5 2031GA Haarlem The Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	TRISENOX 1 mg/ml concentrate for solution for infusion TRISENOX 2 mg/ml concentrate for solution for infusion
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Other antineoplastic agents
	Summary of mode of action: 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-RARα).
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.

Indication(s) in the EEA	**Current (if applicable)**: 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, $\leq 10 \times 10^3/\mu l$) 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-α) gene. The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	**Current (if applicable)**: TRISENOX must be administered under the supervision of a physician who is experienced in the management of acute leukaemias, and the special monitoring procedures must be followed. The same dose is recommended for adults and elderly. **<u>Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL)</u>** *<u>Induction treatment schedule</u>* TRISENOX 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. *<u>Consolidation schedule</u>* TRISENOX 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 acute promyelocytic leukaemia (APL)</u>** <u>Induction treatment schedule</u> TRISENOX 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. <u>Consolidation schedule</u> Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. TRISENOX 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.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current (if applicable)**: TRISENOX 1 mg/ml concentrate for solution for infusion. Type I borosilicate glass ampoule containing 10 ml of concentrate. TRISENOX 2 mg/ml concentrate for solution for infusion. Type I borosilicate glass vial containing 6 ml of concentrate.
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication:

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 $10^3/\mu l$) 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.

Incidence and prevalence

APL is a subtype of acute myeloid leukaemia (AML) with distinctive biologic and clinical features. The disease is relatively rare, accounting for only 10% to 15% of the adults diagnosed with AML (Tallman and Altman, 2009). Recent papers evaluating incidence of haematological malignancies data from 44 European cancer registries (years 2000-2002) report an incidence of 0.14/100,000 for APL and other AMLs with recurrent genetic abnormalities (Sant et al., 2010).

In the UK, approximately 2600 patients are diagnosed with AML annually; this translates to approximately 260 new cases of APL per year (www.cancerresearchuk.org). In Italy, an annual APL incidence of 0.6 per 1×10^6 people have been reported (emedicine.medscape). In the US, the overall annual age-adjusted incidence of APL according to the Surveillance, Epidemiology, and End Results (SEER) database during 1975 to 2008 was 0.18 per 100,000 (0.17 per 100,000 in women and 0.19 in men). The incidence was 0.06 per 100,000 among those aged ≤20 years but increased to 0.36 among those aged ≥60 years (Chen et al., 2012). The incidence of APL appears constant over most of a human lifespan, implying only 1 rate-limiting mutation (Vickers et al., 2000).

Demographics of the target population – age, sex, race/ethnic origin.

According to the European LeukemiaNet, APL is very uncommon in children under 10 years of age. Its incidence increases steadily during the adolescent years, reaches a plateau during early adulthood, and remains constant until it decreases after 60 years of age (Sanz et al., 2009).

The incidence of APL in males and females is equal. Data on an association with race or ethnicity is currently controversial for individuals of Latin origin. High incidence of APL was indicated from observational studies among populations of Latin origin; however, it was also reported that Hispanics did not have greater lifetime APL incidence rates than Caucasians but that the age distribution among Hispanics was significantly different from non-Hispanic

Caucasians, with greater incidence rates for children (1–19 years old) and for adults up to 44 years of age (Douer, 2003; Maule et al., 2008). Among US racial groups, the incidence of APL was 0.18 per 100,000 in whites, 0.16 in other races (American Indians/Alaska Native and Asians/Pacific Islanders) and 0.14 in blacks (Chen et al., 2012).

Risk factors for the disease

Specific risk factors for APL are unknown. The development of AML in general was associated with several risk factors accounting for only a small number of observed cases. These include antecedent hematologic disease, genetic disorders, previous exposure to ionizing radiation, chemotherapeutic agents, and various chemical exposures (e.g. benzene, pesticides, cigarette smoke) (Deschler and Lubbert, 2006).

Main treatment options

The current therapeutic approach uses the all-trans retinoic acid (ATRA) containing regimens for remission induction, plus several cycles of anthracycline-based consolidation chemotherapy. Since the introduction of ATRA the clinically complete remission rate increased up to 90% and cure rates up to 80% (Coombs et al., 2015; Hu, 2011; Lengfelder et al., 2012). Arsenic trioxide (ATO) is also effective in the treatment of APL, resulting in the eradication of APL-initiating cells, and it is currently the agent of choice for treating relapses after initial ATRA-anthracycline therapy (Iland et al., 2012).

Risk stratification is imperative in the treatment of APL patients, as those with low-risk disease (white blood cell count; WBC ≤10 x 103/µl) are generally treated with less intensive regimens than those patients presenting with high-risk disease (WBC >10 x 10^3/µl) (Coombs et al., 2015).

Mortality and morbidity

APL typically presents with potentially life-threatening bleeding complications, as malignant promyelocytes release procoagulant substances, activate the coagulation cascade and deplete fibrinogen, clotting factors, fibrinolytic inhibitors and platelets (Coombs et al., 2015; Lengfelder et al., 2012; Warrell et al., 1993). Haemorrhage represents one of the most frequent causes of early deaths around time of diagnosis and initial treatment phase; it is the main reason why a diagnosis of APL is classified as a medical emergency (Baljevic et al., 2011; Coombs et al., 2015; Kamimura et al., 2011; Park et al., 2011; Sanz et al., 2009). According to the SEER database excess mortality due to APL within 5 years of diagnosis was 36% in 2000–2008 compared to cancer free individuals (Chen et al., 2012).

Important co-morbidities:

Specific information on co-morbidities in patients with either de novo or with refractory or relapsed APL could not be identified from the published literature. The highest incidence of APL is in early adulthood and the prevalence of APL decreases after 60 years of age. Older patients diagnosed with APL may have co-morbidities associated with aging, e.g., cardiovascular disease, arthritis, type 2 diabetes, hypertension and Alzheimer's disease.

Part II: Module SII - Non-Clinical Part of the Safety Specification

The majority of the preclinical data about toxicity and pharmacokinetics comes from published information in the scientific and medical literature and formal reviews by official agencies, including WHO and the US EPA, done as part of their evaluation of the risks to man of arsenical contamination of water and air. Some of those data have been obtained from animal and other laboratory experiments but much has come from the investigation of humans themselves.

The Applicant has undertaken certain basic toxicity tests, which have complied with GLP, but almost all the information critically reviewed here comes from open publications. The compliance of the published work with GLP cannot be ascertained. However, the consistency of the results, the fact that they have been obtained from peer-reviewed scientific publications of a high standard, and that there are searching reviews by eminent experts for national and international official agencies, all of which have arrived at similar conclusion, indicates the available knowledge about the mechanisms of action of arsenical compounds, the doses or concentrations required, and the toxic effects produced can be accepted with confidence.

Table 3: Key Safety Findings (from non- clinical studies) and Relevance to Human Usage

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Toxicology	
Acute toxicity The acute lethality of arsenic trioxide has been determined after *p.o.*, *i.v.*, *i.p.*, and *s.c.* administration (Harrisson *et al.*, 1958). The LD50's in mice were 10.7 *i.v.*, 9.8 to 12.3 *s.c.*, 11.0 to 11.8 *i.p.*, and 39.4 mg/kg *p.o.* In rats, oral LD50 was 15.1 mg/kg.	The acute effects of inorganic arsenic compounds in humans, mainly arsenic trioxide, are well documented. In nearly all cases, the most immediate effects are vomiting, diarrhoea, and gastrointestinal haemorrhage, and death may ensue from fluid loss and circulatory collapse (Levin-Scherz *et al.*, 1987; Saady *et al.*, 1989). The single lethal dose for ingested arsenic in adults is reported to range from 200 to 300 mg (Schoolmeester and White, 1980), with the lowest documented lethal dose being 130 mg (Beliles *et al.*, 1994). Assuming a normal adult body weight of 70 kg, the lethal dose range is approximately 3.9 to 4.3 mg/kg, and the lowest documented lethal dose is 1.9 mg/kg.
Repeat dose toxicity Tests of trivalent arsenic compounds for up to 2 years have been conducted in mice, rats, dogs, and monkeys (Fielder *et al.*, 1986). ***Mice*** In a limited study male mice given 6 mg/kg/day arsenic via the drinking water for 64 days showed a slight reduction in body weight gain and a significant fall in spleen weight (Bencko, 1972). Relative liver weight was reduced early in the study but increased at Day 8 and remained higher than the controls. Metabolic oxygen consumption by liver homogenates was significantly reduced halfway through the study and then recovered.	In general, the systemic toxicological effects resulting from arsenic exposure in animals have been similar to those observed in humans. NOEL values determined from subchronic exposure in mice (0.8 mg/kg/day), chronic exposure in rats (1.7 mg/kg/day), and dogs (0.3 mg/kg/day *i.v.*; 1.25 mg/kg/day *p.o.*), and the minimal toxicities observed in adolescent monkeys receiving 3.75 mg/kg/day provide a safety factor of approximately 2-fold or greater for *i.v.* administration of 0.15 mg/kg/day arsenic trioxide in humans. Oral ingestion of arsenic 0.04 mg/kg/day or higher for several weeks or months can result in overt nonspecific gastrointestinal effects, such as diarrhoea and

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
The no-observable effect level (NOEL) was 0.8 mg/kg/day arsenic. ***Rats*** Newborn rats received arsenic trioxide 5.0, 7.5, or 10 mg/kg by gavage from birth through weaning. They showed increased mortality during the treatment period, low body weight, and increased spontaneous mobility in adulthood (Kiyono *et al.*, 1974). The NOEL was not identified. A study in rats evaluated the subacute effects of arsenic trioxide following *i.p.* administration for a total of 18 days (three cycles of 6 days daily dosing, including a one week observation period between cycles) at dosages of 1, 3, or 9 mg/kg, followed by a 4-week recovery period. Dose-dependent signs of toxicity were observed at all treatment levels and included clinical signs, reduced food consumption, haematological and clinical pathology effects, and histopathological lesions. Repair of the tissues was observed following the recovery period in the 1 and 3 mg/kg treated animals. These toxicological effects are consistent with results reported from other studies of repeated oral or parenteral administration with arsenic trioxide in mice, rats, dogs, and monkeys. ***Dogs*** The effects of arsenic trioxide were evaluated in beagle dogs following *i.v.* infusions for 90 days, followed by a 28-day observation period. No mortalities were observed. The ECG was reported as normal (details of the records are not available). Effects of treatment were observed in the liver, kidney, and testes and hematologic effects on red blood cells occurred at 1.0 and 3.0 mg/kg/day. Arsenic accumulation was observed in the following tissues: brain, lung, heart muscles, liver, intestines, pancreas, spleen, kidney, hair, testis, ovary, muscle, and skin from the area surrounding the injection site. Most of the arsenic-related effects resolved within 28 days following the cessation of treatment. The NOEL was 0.3 mg/kg/day. **Monkeys** Adolescent monkeys receiving 7.5 mg/kg/day developed clinical signs after 5 days, including loss of condition, vomiting, and unformed stools, marked salivation, and uncontrolled head shaking; they were sacrificed on Day 13. Histopathological observations included hepatocyte vacuolisation, decreased glycogen levels in the liver, and dilation of proximal tubules in the kidney. Animals receiving 3.74 mg/kg/day survived to treatment termination. The female developed an unnatural posture of the right arm, but clinical and pathological evaluations showed no other significant findings.	cramping. Sensory neuropathy can also occur after months to years of arsenic exposure at this level. These effects generally resolve slowly on cessation of exposure (NRC, 1999). The extent of toxicity resulting from arsenic trioxide or sodium arsenite treatment is dependent upon the dose and duration of exposure. The relevance of accumulation potential of arsenic trioxide to human remains unknown.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Cardiac effect Chiang et al (2002) conducted a study to determine the effect of arsenic trioxide on the guinea pig heart (Au and Kwong, 2008; Chiang *et al.*, 2002). Papillary muscle was perfused with increasing concentrations of arsenic trioxide and then electrically stimulated with increasing frequencies (0.1 or 2 Hz). This test showed a dose-dependent prolongation of the action potential duration at the lower frequency. In an *in vivo* system, *i.v.* and other parenteral routes of administration of arsenic trioxide to guinea pigs had little or no effect on heart rate, but arsenic trioxide prolonged the QT interval in a time- and dose-dependent manner. In addition, arsenic trioxide treatment prolonged the action potential duration of the guinea pig hearts.	Prior to initiating therapy an ECG must be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine must be assessed; preexisting electrolyte abnormalities must be corrected and, if possible, medicinal products that are known to prolong the QT interval must be discontinued. Patients with risk factors of QTc prolongation or risk factors of torsade de pointes should be monitored with continuous cardiac monitoring (ECG).
Nephrotoxicity Renal effects have been demonstrated in mice, rats and adolescent monkeys. Li et al (2010) evaluated the oxidative DNA damage in kidney tissue of mice exposed to arsenic trioxide subchronically by observing the expression of 8-hydroxy-2- deoxyguanosine (8-OHdG) and pathologic changes (Li *et al.*, 2010). Forty mice were randomly divided into 4 groups of 10 each (5 mice of each sex). Group 1 received drinking water alone (control) and Groups 2, 3 and 4 received 1, 2 and 4 mg/L arsenic trioxide, respectively. Arsenic trioxide was given through drinking water for 60 days. The expression of 8-OHdG in the kidney tissue of mice was analysed in these 4 groups. The groups treated with arsenic trioxide showed pathologic changes in the kidney tissue and significant increase in the level of 8-OHdG expression ($p < 0.01$). Moreover, the dose-dependent increase between arsenic trioxide exposure and renal damages were observed. Especially, its immuno-activity was strong in the proximal convoluted tubule and Bowman's capsule. These results suggest that chronic exposure to arsenic trioxide induces damages to kidney tissue, and especially the epithelial cells of proximal convoluted tubule and the podocytes of the Bowman's capsule may be more sensitive to arsenic trioxide-induced nephrotoxicity.	*Renal Insufficiency* Plasma clearance of As^{III} was not altered in patients with mild renal impairment (creatinine clearance of 50-80 mL/min) or moderate renal impairment (creatinine clearance of 30-49 mL/min). The plasma clearance of As^{III} in patients with severe renal impairment (creatinine clearance less than 30 mL/min) was 40% lower when compared with patients with normal renal function. Systemic exposure to MMA^{V} and DMA^{V} tended to be larger in patients with renal impairment; the clinical consequence of this is unknown but no increased toxicity was noted.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Hepatotoxicity The principal toxic effects in animals and man are acute GI damage, after very high oral doses, with associated clinical signs, liver damage, and sometimes seizures.	A number of studies in humans exposed to inorganic arsenic by chronic oral ingestion at 0.019 - 0.1 mg As/kg/day have noted features of hepatic injury characterised by a swollen and tender liver and elevated levels of hepatic enzymes. There has been portal tract fibrosis, leading in some cases to portal hypertension (PHS, 1993). *Hepatic Insufficiency* Pharmacokinetic data from patients with hepatocellular carcinoma having mild to moderate hepatic impairment indicate that AsIII or AsV do not accumulate following twice-weekly infusions. No clear trend toward an increase in systemic exposure to AsIII, AsV, MMAV or DMAV was observed with decreasing level of hepatic function as assessed by dose-normalised (per mg dose) AUC. The warnings and precautions section of the SmPC advises that patients with severe renal and/or hepatic impairment should be closely monitored for toxicity when treated with TRISENOX.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Carcinogenicity / Mutagenicity Carcinogenicity studies were not conducted by the Applicant and are normally not required for anticancer agents such as TRISENOX™. Arsenic is accepted as a proven human carcinogen, but the available evidence suggests that there may well be a threshold dose below which it will not have that action; perhaps a few hundred micrograms per day in the diet (NRC, 1999). Again, that has clinical implications. The results of genetic toxicity testing have been difficult to interpret. It is likely that arsenic trioxide, although a proven mutagen in mammalian cell systems, but not in the Ames test, may act by disturbing DNA repair mechanisms rather than as a direct genotoxic agent. That suggests the possibility of a threshold exposure below, which there might not be any genotoxic effect (NRC, 1999). Arsenite and arsenic trioxide can be mutagenic in mammalian cells in culture, and a positive bone marrow micronucleus test has been reported. A dominant lethal test was negative. The mechanism of the genotoxicity is not clear, as the conventional Ames test, for example, has usually given a negative result. The effects produced represent chromosomal damage and deletions and not simple point mutations 10. Simultaneous exposure to arsenite and a genotoxicant drug may enhance the DNA damaging effect of the latter, and so may increase the risk of subsequent carcinogenicity. Such a combination requires caution in clinical work, depending on the nature of the disease to be treated.	No formal carcinogenicity studies of arsenic trioxide have been performed. However, arsenic trioxide and other inorganic arsenic compounds are recognised as human carcinogens. Arsenic compounds induce chromosomal aberrations and morphological transformations of mammalian cells *in vitro* and *in vivo*. Potential for the development of secondary cancers. This is a risk for nearly all chemotherapeutic drugs. “
Embryotoxicity and teratogenicity Reproductive toxicology studies were not conducted by the Applicant and are normally not required for anticancer agents such as TRISENOX™. Nevertheless, reproductive toxicity testing of inorganic arsenicals has been done by various groups and complex and sometimes conflicting results have been obtained. The overall pattern of findings shows that these compounds are teratogenic and cause maternal and fetal toxicity in the mouse and rat but not in the rabbit. They do not affect female fertility. Male fertility has not formally been tested.	Arsenic trioxide has been shown to be embryotoxic and teratogenic in animal studies. In humans, the effect of arsenic on fertility has not been adequately studied; there are no studies in pregnant women using TRISENOX. Because of the potential for foetal harm, women of childbearing potential should avoid becoming pregnant while taking TRISENOX and for 6 months following completion of treatment. Men should use effective contraceptive measures and be advised to not father a child while receiving TRISENOX and for 3 months following completion of treatment.
General safety pharmacology	
Mechanisms for drug interactions Since methylation of arsenic is a detoxification mechanism, it is possible that chemicals which interfere with the methylation process could increase toxicity.	No formal assessments of pharmacokinetic interactions between TRISENOX and other therapeutic medicinal products have been conducted. QT/QTc prolongation is expected during treatment with TRISENOX, and

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Studies in animals showed that reagents that inhibit the methylation enzymes (e.g. PAD) caused an increase in tissue levels of iAs. Similarly, cellular GSH levels appear to play a role in the methylation process, and treatment with reagents (e.g. phorone) that decrease GSH levels increases arsenic toxicity.	torsade de pointes and complete heart block have been reported. Patients who are receiving, or who have received, medicinal products known to cause hypokalaemia or hypomagnesaemia, such as diuretics or amphotericin B, may be at higher risk for torsade de pointes. Caution is advised when TRISENOX is co-administered with other medicinal products known to cause QT/QTc interval prolongation such as macrolide antibiotics, the antipsychotic thioridazine, or medicinal products known to cause hypokalaemia or hypomagnesaemia.
Other toxicity-related information or data Arsenical salt (7.33% arsenic trioxide equivalent), 0, 3.74, or 7.5 mg/kg/day As_2O_3 suspended in a milk supplement, was orally administered to infant and adolescent rhesus monkeys for 52 weeks (Heywood and Sortwell, 1979). Deaths were observed in the infant monkeys of both treatment groups due to acute bronchopneumonia with lung haemorrhage, oedema, and necrosis with aggregations of inflammatory cells in the brain and spinal cord in one animal on 3.74 mg/kg/day. A male in the 7.5 mg/kg/day group that died on day 17 displayed acute inflammation and haemorrhagic areas in the small intestine, and a 3.74 mg/kg/day female that died on day 24 had some atrophy of the thymus. For animals that died on Days 128 and 273, the cause of death was not determined. Animals surviving to sacrifice at the end of treatment showed very few signs of treatment-related toxicity.	Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, breastfeeding must be discontinued prior to and throughout administration and for two weeks after the last dose.

Part II: Module SIII - Clinical Trial Exposure

As of 30 September 2015, estimated cumulative clinical trials exposure to ATO in 11 clinical trials was approximately 363 patients; 6 clinical trial(s) were sponsored by Cephalon, Inc. (CTI 1073, CTI 1058, CTI 1061, ATO202, CTI 1064, C18477/3059/AM/US-CA and 5 clinical trials were sponsored by Cell Therapeutics, Inc. (CTI1057, CTI1059, CTI1060, CTI1062, CTI1063). The MAH (Teva) is aware that the cumulative number of patients exposed to arsenic trioxide in all clinical trials sponsored by MAHs (Cephalon, Inc. /CTI) prior the acquisition by Teva Group may be higher since, due to the historical reasons, much of the data regarding studies conducted with ATO became only limitedly available to Teva.

In addition, two studies, APL0406 and AML-17, were conducted by independent groups (Gruppo Italiano Malattie Ematologiche dell'Adulto; GIMEMA) in the indication newly diagnosed low-to-intermediate risk APL (WBC count $\leq 10 \times 10^3/\mu l$) in combination with all trans retinoic acid (ATRA). Overall, 215 patients (low to intermediate risk) were exposed to ATO in these studies. As Teva is not the owner of the data, and only one study is published (Lo-Coco *et al.*, 2013), the available exposure data is limited.

Table 4: Exposure to arsenic trioxide by study

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
INDICATION: Patients *with newly diagnosed low-to-intermediate risk APL (WBC count ≤ 10 × 10^3/µl) in combination with all trans retinoic acid (ATRA)*					
	APL0406 (Lo-Coco *et al.*, 2013; Lo-Coco *et al.*, 2015 accepted for publication; Platzbecker *et al.*, 2014 abstract)	77 core study 129 extended cohort (includes 77 patients from core study)	Induction: ATO 0.15 mg/kg/dose daily until bone marrow remission or until a maximum of 60 doses Consolidation: Patients with CR received same dose ATO 5 days per week, 4 weeks on and 4 weeks off for a total of 4 courses	Not available Estimated 140 doses maximum (total of 21 mg/kg) per patient maximum	Not available Not available
	AML-17 (Burnett *et al.*, 2015)	86 *Note: 116 included in study, out of which 30 were high risk patients*	Induction: ATO *i.v.* at 0.3 mg/kg on day 1-5 daily and then twice per week at 0.25 mg/kg until complete remission or day 60 Consolidation: ATO was given at the same doses for days 1-5 (0.3 mg/kg) and then twice per week for 3 weeks (0.25 mg/kg) for 4 courses	Not available Estimated 48 doses maximum (total 17 mg/kg) per patient maximum	Not available
INDICATION: Patients with relapsed or refractory acute promyelocytic leukaemia					
	PLRXAS01 (Pivotal) *PLRXAS02* (*Maintenance treatment study not supporting the primary indication – including 18 out of 40 patients*)	40	Induction: ATO 0.15 mg/kg/dose daily until bone marrow remission or until a maximum of 60 doses Consolidation: Patients with CR received 25 doses at the same dose as used during induction *Maintenance: Up to 4 courses of treatment with ATO given consecutively or on weekdays only for a cumulative total of 25 days per course.* *Absent disease progression, subsequent courses could be administered after a break of 4 to 6 weeks*	84.0	4410

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
	97-66 97-66 PK *98-13* *(Maintenance treatment study not supporting the primary indication – including 7 out of 12 patients)*	12	Induction: 6 patients received 10 mg ATO per dose; 3 received 15 mg/dose, 1 received 5 mg/dose and 2 received 0.15 mg/kg/dose daily until bone marrow remission or a maximum of 60 doses Consolidation: Patients with CR received 25 doses at the same dose as used during induction *Maintenance: Up to 4 courses of treatment with ATO given consecutively or on weekdays only for a cumulative total of 25 days per course.* *Absent disease progression, subsequent courses could be administered after a break of 4 to 6 weeks.*		
SUPPORTIVE: acute promyelocytic leukaemia compassionate use programs					
	Special Exception Program (NCI)	17	Induction: ATO 0.15 mg/kg daily for up to 60 days or until complete remission Consolidation: Patients who achieved CR received 1 to 4 consolidation/ maintenance courses with ATO 0.15 mg/kg administered for up to 25 or 28 days per course	NA	NA
	ATU	2	Induction: ATO 0.15 mg/kg daily for up to 60 days or until complete remission Consolidation: Patients who achieved CR received 1 to 4 consolidation/ maintenance courses with ATO 0.15 mg/kg administered for up to 25 or 28 days per course	NA	NA

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
	Ohno, Japan	8	Induction: ATO 0.15 mg/kg daily for up to 60 days or until complete remission Consolidation: Patients who achieved CR received 1 to 4 consolidation/ maintenance courses with ATO 0.15 mg/kg administered for up to 25 or 28 days per course	NA	NA
	Avvisati, Italy	9	Induction: ATO 0.15 mg/kg daily for up to 60 days or until complete remission. Consolidation: Patients who achieved CR received 1 to 4 consolidation/ maintenance courses with ATO 0.15 mg/kg administered for up to 25 or 28 days per course	NA	NA
Other studies with patients with acute promyelocytic leukaemia					
	Study T99-0080	13	Administered i.v. over 2 hours, 5 d/wk for 20 doses/cycle. Patients with APL (n=13) received 0.15 mg/kg per day.	56.9	NA
	CALGB C9710 ATO 101	200 (patients receiving the consolidation treatment including ATO)	Induction therapy: ATRA: 45 mg/m^2/day (22.5 mg/m^2 twice daily), p.o., on day 1 until CR or day 90 Cytarabine: 200 mg/m^2/day (continuous i.v. infusion) for 7 days (days 3 through 9) Daunorubicin: 50 mg/m^2 i.v. bolus daily for 4 days (days 3-6) Consolidation therapy: ATRA/Chemo therapy: ATRA at 45 mg/m^2/day (22.5 mg/m2 twice daily), p.o., for 7 days. Daunorubicin: 50 mg/m^2	47.4	18945

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
			i.v. bolus daily (days 1-3) (Note: Patients were randomly assigned to receive this treatment or arsenic trioxide therapy after induction therapy.) ATRA/Chemo/ATO therapy: 0.15 mg/kg i.v. daily, administered as a 2-hour i.v. infusion 5 days/week for 5 weeks for 2 cycles followed by 2 cycles of consolidation therapy with ATRA/Chemo Maintenance therapy: (Note: Patients who completed consolidation therapy and remained in CR were randomly assigned to 1 year of intermittent ATRA at 45 mg/m2/day (22.5 mg/m^2 twice daily), p.o., for 7 days with or without 6-mercaptopurine (60 mg/m^2 daily, p.o.) and methotrexate (20 mg/m^2 weekly) for 2-4 weeks after final consolidation therapy		
Advanced refractory or relapsing leukaemia					
	98-23 98-23 PK	24	ATO was administered at 0.10 to 0.35 mg/kg/dose i.v. daily for a minimum of 25 consecutive days. Injection administered as 1 to 2-hour infusion; infusion duration may be extended up to 4 hours if acute vasomotor reactions observed. Treatment cycle for up to 25 days, additional 25-day cycles at the investigator's discretion.	27.0	720
	DM98-211	16	0.15 mg/kg; ATO was provided as a 1 mg/mL solution in 10 mL	NA	NA

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
			ampoules. Drug was diluted in 250 mL DSW before intravenous infusion over 1 to 2 hours		
Solid Tumours					
Non-haematological cancers	98-46 98-46 PK	34	Six patients received 0.15 mg/kg / dose; 3 received 0.20 mg/kg/dose; 4 received 0.25 mg/kg/dose; 6 received 0.30 mg/kg/dose; and 3 received 0.35 mg/kg/dose. Treatment was administered daily in 5-day cycles, with only 1 cycle administered per month	8.4	748
Prostate cancer	ATO 202	7	ATO: 0.25 mg/kg/day 5 days in week 1, twice weekly thereafter Docetaxel: 35mg/m^2/week for 6 weeks, for each 8-week cycle; 2 cycles total	38.4	859
Neuroblastoma and other solid tumors	CTI 1059	20	0.25 mg/kg/day, days 1-5 and 8-12, 4-week cycle; 6 cycles of treatment	24.5	1447
	CTI 1064	29	0.25- 0.50 mg/kg/day 2 days/week for 6-weeks, for each 8-week cycle; up to 6 cycles of treatment.	15.5	2272
	CTI 1073	20	0.15 mg/kg/day 2 days/week for 4 weeks, for each 6-week cycle	10.7	871
Multiple Myeloma					
	UARK 98-03	14	0.15 mg/kg; ATO in 500 mL of 5% dextrose administered i.v. over 1 to 2 hours daily until bone marrow remission, to a cumulative total of 60 days	NA	NA
	CTI 1057	24	0.25 mg/kg/dose i.v. (1-4h), 4-week	31.7	1949

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
			treatment cycles (5 doses/week for 2 weeks followed by 2 weeks with no study drug treatment) Six 4-week cycles of treatment; 1 patient was treated for nineteen 4-week cycles		
	CTI 1060	11	ATO: 0.25 mg/kg/day 5 days in weeks 1and 2 Dexamethasone: 40 mg/day, for 5 days Every 4 weeks	25.0	844
	CTI 1062	14	0.30 mg/kg/day, 5 days in week 1, 0.25 mg/kg/day twice weekly thereafter for a minimum of 15 additional weeks	29.6	2446
	CTI 1063	16	0.25 or 0.35 mg/kg/day, 2 days/week for 8 weeks, for each 11-week cycle	23.1	1603
Myelodysplastic Syndromes					
	CTI 1058	70	0.25 mg/kg/day, days 1-5 and 8-12, 4-week cycle	32.3	7056
	CTI 1061	115	0.30 mg/kg/day 5 days in week 1, 0.25 mg/kg/day twice weekly thereafter	29.5	10913
Elderly patients with acute myeloid leukemia					
	C18477-3059-AM-US-CA	33 (patients who received LDAC + ATO)	ATO: 0.25 mg/kg/day, days 1-5 and 8-12 (1 to 2 induction cycles up to 70 days;1 to 14-day consolidation cycle) and 0.25 mg/kg days 1 and 4 (each 28-day maintenance cycle) LDAC: 10 mg/m^2 b.i.d, days 1-14 (1-2 induction cycles up to 70 days; 1 to 14-day consolidation cycle) and 10 mg/m^2 b.i.d, days 1-7 (each 28-day maintenance cycle)	19.2	NA

Indication	Study number	Number of patients	Dosage	Number of doses (Mean)	Exposure by patient-day
Total number of patients in 11 clinical trials for current indication		749	**Total exposure**	36.7 doses/ patient [a]	55,083 patient-day [b]

[a] Mean number of doses administered per patient, based on available clinical data. Please note that data from compassionate use and legacy data from 2 studies (UARK 98-03, DM 98-211) did not include number of doses administered to the patients (i.e. 66 out of 749 patients).

[b] Exposure by patient-day is based on available clinical data on ATO treatment duration. Please note that data from compassionate use and legacy data from 4 studies (C18477-3059- AM-US-CA, UARK 98-03, DM-98-211, T99-0080) didn't include any information on treatment duration. This concerns 99 out of 749 patients.

Table 5: Clinical Patient Exposure to study medication by Gender

Indication	Male	Female
Newly diagnosed APL	160[a]	162[a]
Relapsed or refractory APL	106	94
Hepatocellular carcinoma	22	7
Adult cancer patients with renal dysfunction	12	8
Multiple myeloma	37	28
Myelodysplastic syndromes	134	51
Neuroblastoma and other solid tumours	14	6
Prostate cancer	7	0
Non-haematological cancers	21	13
Acute myeloid leukaemia	17	16
Total	**410**	**260**

[a] Includes gender data for (Burnett et al., 2015; Lo-Coco et al., 2013) – Number of patients (male and female) also include 30 high risk patients in the Burnett study

Table 6: Clinical Patient Exposure to study medication by Age Group

Indication	Age range (yrs)	Number of patients
Newly diagnosed APL (extended indication)	(Lo-Coco *et al.*, 2013; Platzbecker *et al.*, 2016 submitted for publication; Platzbecker *et al.*, 2014 abstract) 18-71	129
	(Burnett *et al.*, 2015) 16-29 30-59 ≥60	[a] 22 69 25
Relapsed or refractory APL	5-20	23

Indication	Age range (yrs)	Number of patients
	21-75 76-80	174 3
Hepatocellular carcinoma	24-87	29
Adult cancer patients with renal dysfunction	29-85	20
Multiple myeloma	41-83	65
Myelodysplastic syndromes	31-93	185
Neuroblastoma and other solid tumours	4-36	20
Prostate cancer	59-70	7
Non-haematological cancers	8-75	34
Acute myeloid leukaemia	61-83	33
Total		**908**

[a] Note: number of patients include 30 high risk patients (total 116 who participated in the study); only 86 patients were low/intermediate risk, however, age categories data is not available for these low-intermediate patients

Exposure by Race

The majority (75%) of enrolled patients were Caucasian which is representative of target population. Black, Hispanic and Islander patients accounted for 13, 8 and 5%, respectively.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 7: Important Exclusion Criteria in the Pivotal Clinical Studies within the Development Programme

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Hypersensitivity to the active substance or any of the excipients	Arsenic trioxide is contraindicated in patients with known hypersensitivity to the active substance(s) or to any of the excipients	No	Hypersensitivity to the active substance or any of the excipients will remain as a contraindication.
Breastfeeding	Because arsenic is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from arsenic trioxide, breastfeeding must be discontinued prior to and throughout administration.	No	As explained in SmPC section 4.6 breastfeeding must be discontinued prior to and throughout administration and for two weeks after the last dose.

Pregnancy	There are no adequate data from the use of arsenic trioxide in pregnant women. Pregnancy is a typical exclusion criterion in clinical trials.	No	As explained in SmPC section 4.6 women of childbearing potential and men must use effective contraception during treatment with arsenic trioxide and for 6 months following completion of treatment. Men should use effective contraceptive measures and be advised to not father a child while receiving TRISENOX and for 3 months following completion of treatment.
Significant arrhythmias, ECG abnormalities[a]	Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal.	No	As explained in SmPC section 4.4 prior to initiating therapy an ECG must be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine must be assessed; preexisting electrolyte abnormalities must be corrected and, if possible, medicinal products that are known to prolong the QT interval must be discontinued. Patients with risk factors of QTc prolongation or risk factors of torsade de pointes should be monitored with continuous cardiac monitoring (ECG).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Children	The experience in children is limited. Out of 7 patients less than 18 years of age (range 5 to 16 years) treated with TRISENOX at the recommended dose of 0.15 mg/kg/day, 5 patients achieved a complete response. No data are available for children under 5 years. In an additional study, the toxicity profile observed in 13 paediatric patients with APL between the ages of 4 and 21 receiving ATO at 0.15 mg/kg/day was similar to that observed in adult patients (Fox *et al.*, 2008). Safety and effectiveness in relapsed APL paediatric patients below the age of 4 years have not been studied.
Elderly	There is limited clinical data on the use of ATO in elderly patients (> 65 years of age) with relapsed or refractory APL. Caution is needed in these patients. The pivotal study PLRXAS01 (relapsed settings) included 12.5% of elderly patients. In first line settings (proposed indication), in the original cohort of study APL0406, 16 patients aged between 60 and <71 years were assigned to ATRA + ATO (Lo-Coco *et al.*, 2013). Study AML-17 included 21.6% of patients (49 patients, of whom 37 were low risk) over the age of 60 years of age with newly diagnosed APL; the number of patients who received ATRA + ATO is unknown (Burnett *et al.*, 2015).
Pregnant or Breast-Feeding Women	No pregnancies were observed in the pivotal clinical trial for the current indication. However, arsenic trioxide has been shown to be embryotoxic and teratogenic in animal studies. There are no adequate and well controlled studies of arsenic trioxide in pregnant women. Therefore, women of childbearing potential are advised to avoid becoming pregnant while taking arsenic trioxide and for 6 months following completion of treatment. These patients are advised that they must use effective contraception throughout treatment period and for 6 months afterward. Men are also advised to use effective contraception during treatment with arsenic trioxide and for 3 months following completion of treatment. Furthermore, because arsenic is excreted in human milk and because of its potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Patients are advised not to breastfeed during treatment with arsenic trioxide and for two weeks after the last dose. No clinical or non-clinical fertility studies have been conducted with ATO.

Type of special population	Exposure
Patients with hepatic impairment	No formal studies have been conducted in patients with hepatic impairment. Much of the As^{III} is distributed to the tissues where it is methylated to the less cytotoxic metabolites, MMA^{V} and dimethylarsinic acid DMA^{V} by methyltransferases primarily in the liver. In study PLRXAS01 relapsed patients were required to have adequate hepatic function; this was defined as serum bilirubin < 2.5 times the upper limit of normal. Patients with severe hepatic impairment (Child-Pugh class C) should be closely monitored for toxicity when treated with ATO. In study APL0406, newly diagnosed low-intermediate risk patients were required to have total bilirubin ≤ 3.0 mg/dl (or ≤ 51µmol/l) (Lo-Coco *et al.*, 2013) and for study for study AML-17 serum total bilirubin ≤ 2 mg/dl for inclusion (Burnett *et al.*, 2015).
Patients with renal impairment	No formal studies have been conducted in patients with renal impairment. Approximately 15% of the administered arsenic trioxide dose is excreted in the urine as unchanged As^{III}. The methylated metabolites of As^{III} (MMA^{V}, DMA^{V}) are primarily excreted in the urine. In both study APL0406 and study AML-17, patients were required to have adequate renal function at baseline to allow for reasonable clearance of the drug; this was defined as serum creatinine ≤ 3.0 mg/dL (≤ 265 µmol/L) (Lo-Coco *et al.*, 2013) and serum creatinine < 3.0 mg/dL (< 260 µmol/L) (Burnett *et al.*, 2015). Since no data are available across all renal impairment groups, caution is advised in the use of ATO in patients with renal impairment. The experience in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) is insufficient to determine if dose adjustment is required. ATO has not been adequately studied in patients with severe renal impairment or end stage renal disease.

Type of special population	Exposure
Patients with cardiac impairment	Patients with cardiac impairment were not excluded in the pivotal clinical trial, however they were excluded in the two studies with extended indication (Burnett *et al.*, 2015; Lo-Coco *et al.*, 2013). ATO treatment is associated with cardiac effects. QT/QTc prolongation and torsade de pointes as well as complete heart block have been reported with arsenic trioxide treatment. In clinical trials, in the relapsed/refractory setting, 16 of 40 patients (40%) experienced at least one QT corrected (QTc) interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after ATO infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age. One patient (also receiving amphotericin B) had torsade de pointes during induction therapy for relapsed APL with ATO. In 77 newly diagnosed APL patients 12 (15.6 %) showed QTc prolongation with arsenic trioxide in combination with retinoic acid. In one newly diagnosed patient induction treatment was terminated because of severe prolongation of the QTc interval and electrolyte abnormalities on day 3 of induction treatment. Prior to initiating therapy with ATO, a 12-lead ECG must be performed, and serum electrolytes (potassium, calcium, and magnesium) and creatinine must be assessed; pre-existing electrolyte abnormalities must be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. Patients with risk factors of QTc prolongation or risk factors of torsade de pointes should be monitored with continuous cardiac monitoring (ECG). For QTc greater than 500 msec, corrective measures must be completed and the QTc reassessed with serial ECGs and, if available, a specialist advice could be sought prior to considering using ATO. During therapy with ATP, potassium concentrations must be kept above 4 mEq/l and magnesium concentrations must be kept above 1.8 mg/dl. Patients who reach an absolute QT interval value > 500 msec must be reassessed and immediate action must be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending ATO therapy must be considered. If syncope, rapid or irregular heartbeat develops, the patient must be hospitalised and monitored continuously, serum electrolytes must be assessed, ATO therapy must be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. After recovery, treatment should be resumed at 50 % of the preceding daily dose. If QTc prolongation does not recur within 7 days of restarting treatment at the reduced dose, treatment with ATO can be resumed at 0.11 mg/kg body weight per day for a second week. The daily dose can be escalated back to 100% of the original dose if no prolongation occurs. There are no data on the effect of ATO on the QTc interval during the infusion. Electrocardiograms must be obtained twice weekly, and more frequently for clinically unstable patients, during induction and consolidation.

Type of special population	Exposure
Patients with disease severity different from the inclusion criteria studied in clinical trials	Patients with newly diagnosed APL have not been systematically studied by the Applicant, i.e., the Applicant did not conduct pivotal studies in first line therapy of APL with ATO.
Patients of Different Racial and/or Ethnic Origin	In clinical trials, in the relapsed/refractory setting, the majority (75%) of enrolled patients were Caucasian which is representative of target population. Black, Hispanic and Islander patients accounted for 13, 8 and 5%, respectively. No information on race is available for the two studies (APL0406 and AML-17) in the indication newly diagnosed APL patients.

Part II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Estimation of cumulative exposure from post-marketing sources was calculated based on data collected from Teva and acquired companies available since 2002.

According to the World Health Organisation (WHO, ATC/DDD Index, 2020), no Defined Daily Doses (DDDs) have been established for antineoplastic agents (including arsenic trioxide) because of highly individualised use and wide dosage ranges. The doses used vary substantially because of various types and severity of neoplastic diseases, and also because of the extensive use of combination therapy. The consumption of the antineoplastic agents is in some countries measured in grams. This is recommended as a method to be used internationally for these particular agents.

Given the variability in therapy duration—particularly during the consolidation phase for both first-line and refractory APL—estimating the number of patients exposed to Teva Group products containing arsenic trioxide is challenging. Therefore, exposure is expressed in terms of the total grams of arsenic trioxide sold, representing the estimated market experience.

SV.1.2 Exposure

Cumulatively, until the 30 April 2025 it is estimated that exposure to Teva Group products containing arsenic trioxide amounts to approximately 28,832 grams sold.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Although several cases of intentional (suicide attempts), criminal (homicidal) and accidental arsenic trioxide poisoning ingestion are reported in the literature, no cases of *i.v.* arsenic trioxide misuse have been reported.

Arsenic trioxide has no addictive potential such as dependence and tolerance, thus the potential for misuse for illegal purposes is negligible. Based on the nature and pharmacological effects of TRISENOX, there is no foreseen potential for misuse or abuse.

TRISENOX is not considered of having any potential for misuse for illegal purposes.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Table 9: Summary of Safety Concerns in the initial RMP (version 1.3; approval date 14 November 2016)

Summary of Safety Concerns	
Important identified risks	• Leukocyte Activation Syndrome (APL Differentiation Syndrome) • Blood dyscrasias (including hyperleukocytosis) • Electrocardiogram (ECG) Abnormalities such as QT/QTc interval prolongation and complete atrioventricular block • Liver enzyme elevation
Important potential risks	• Embryotoxic and teratogenic effect in pregnancy • Serious adverse reactions in nursing infants • Carcinogenicity
Important potential Drug Interaction	Potential interactions of arsenic trioxide with: • Drugs known to cause hypokalaemia or hypomagnesaemia • Drugs known to cause QT/QTc prolongation
Missing information	• Influence on fertility • Use in paediatric patients under the age of 4 years • Use in patients with renal impairment • Use in patients with hepatic impairment • Long-term safety

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety concerns ‘Carcinogenicity’ and ‘Long-term safety’ are removed from the list of safety concerns.

Reasons for the removal from the list of safety concerns in RMP v3.0:

The important potential risk of carcinogenicity (secondary malignancy) has been re-evaluated based on the new evidence provided by the PASS results. The study findings demonstrated that the incidence of secondary malignancies in the treated population was significantly lower (1.10%) than the expected incidence in the relevant population, according to literature source incidence which was included in the protocol (2%). There were no emerging safety signals or

trends observed. Therefore, it can be concluded that the risk is adequately characterized, no longer considered an important one and can be removed from the list of safety concerns in the RMP.

Based on the results noted in the final study report of Post-Authorisation Long-Term Retrospective Safety Cohort Study of ATO in First Line Low- to Intermediate-Risk APL patients, no new safety concerns were raised regarding the use of ATO in combination with ATRA in the authorised indication.

The available results of this study are generally in line with what has been observed in clinical trials and the known safety profile of ATO described within the product information.

Based on the above, safety of ATO+ATRA on long-term use in newly diagnosed low-to-intermediate risk APL patients has been confirmed in this PASS.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Table 10: Important Potential Risk: Medication errors caused by confusion between the different concentrations

Medication errors caused by confusion between the different concentrations	
Potential mechanisms	Not applicable
Evidence source(s) and strength of evidence	No data regarding this potential risk is currently available, however a risk of medication errors caused by confusion between the different concentrations cannot be excluded if different presentations are available in the market.
Characterisation of the risk	There is a theoretical potential for a medication error if a healthcare professional uses the newly introduced vial presentation instead of the ampoule presentation without considering the differences in concentration. The vial presentation contains double the concentration of arsenic trioxide compared to the concentration of arsenic trioxide contained in the ampoules. It is anticipated that, in case of confusion between the two presentations, under-dosing or over-dosing related events may appear provided the error is not intercepted. The severity of the reactions would likely be dependent on the total dose erroneously administered.
Risk factors and risk groups	Underlying systems factors have been seen to be contributors to the occurrence of medication errors (Keers et al, 2013). Human factors such as high perceived workload, staff health status (fatigue, stress) or interruptions/distractions during drug administration, and problems with ward-based equipment (access, functionality) have been reported as medication error general causes (Keers et al, 2013). Regarding the specific *i.v.* medication error risk, a study conducted at a paediatric hospital that was using automated compounding identified four factors that were significantly ($p < 0.05$) associated with an increased risk of compounding errors in this setting: Dose preparation during the morning shift (relative risk [RR], 1.84; 95% CI, 1.68-2.02) or on a Sunday (RR, 1.28; 95% CI, 1.11-1.47), preparation of doses for use in critical care units (RR, 1.17; 95% CI, 1.07-1.28), and technician versus pharmacist compounding (RR, 1.17; 95% CI, 1.04-1.32) (Deng et al, 2016).

Medication errors caused by confusion between the different concentrations	
Preventability	Clear communication of the newly available strength to the healthcare professional involved in preparation of the diluted solution for infusion, including prominent labelling.
Impact on the risk-benefit balance of the product	Since this risk is potential only, the impact on the risk-benefit balance, if any, cannot be predicted.
Potential public health impact of safety concern	The frequency of this risk and thus the number of possibly affected patients and the public health impact cannot be anticipated.

Part II: Module SVIII - Summary of the Safety Concerns

Table 11: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Medication errors caused by confusion between the different concentrations
Missing information	• None

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Not applicable.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 12: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Medication errors caused by possible confusion between the different concentrations	**Routine risk communication:** Clear quantitative composition is given in SmPC, PL, outer packaging and immediate packaging. On the outer and immediate vial packaging a red box warning highlighting the new concentration will appear for at least 6 months from launch in each European Union country. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 13: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors caused by possible confusion between the different concentrations	**Routine risk minimisation measures:** Clear quantitative composition is given in SmPC, PL, outer packaging and immediate packaging. On the outer and immediate vial packaging a red box warning highlighting the new concentration will appear for at least 6 months from launch in each European Union country. Prescription only medicine. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for TRISENOX (arsenic trioxide)

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

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

This summary of the RMP for arsenic trioxide 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´s RMP.

I. The Medicine and What It is used for

TRISENOX is authorised for induction of remission, and consolidation in adult patients with acute promyelocytic leukaemia (APL) (see SmPC for the full indication). It contains arsenic trioxide as the active substance, and it is given as an infusion into a vein.

Further information about the evaluation of TRISENOX´s benefits can be found in TRISENOX´s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/trisenox

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of arsenic trioxide, together with measures to minimise such risks and the proposed studies for learning more about arsenic trioxide´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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of TRISENOX 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 TRISENOX. 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	• Medication errors caused by confusion between the different concentrations
Missing information	• None

II.B Summary of Important Risks

Table 14: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important potential risk: Medication errors caused by confusion between the different concentrations	
Evidence for linking the risk to the medicine	The product is authorised in 2 different presentations: • 10 mg/10 ml (1 mg/1 ml) of arsenic trioxide in a glass ampoule. • 12 mg/6 ml (2 mg/ ml) in a vial. There is a low theoretical potential for a medication error if a healthcare professional use the vial presentation instead of the ampoule presentation without considering the differences in concentration.
Risk factors and risk groups	Underlying systems factors have been seen to be contributors to the occurrence of medication errors. Human factors such as high perceived workload, staff health status (fatigue, stress) or interruptions/distractions during drug administration, and problems with ward-based equipment (access, functionality) have been reported as medication error general causes.
Risk minimisation measures	**Routine risk minimisation measures:** Clear quantitative composition is given in SmPC, PL, outer packaging and immediate packaging.

Important potential risk: Medication errors caused by confusion between the different concentrations	
	On the outer and immediate vial packaging a red box warning highlighting the new concentration will appear for at least 6 months from launch in each European Union country. Prescription only medicine. **Additional risk minimisation measures:** None.

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 TRISENOX.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for TRISENOX.

Part VII: Annexes

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Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.