SUMMARY OF PRODUCT CHARACTERISTICS

ARSENIC TRIOXIDE S.K. 1mg/ml concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

ARSENIC TRIOXIDE S.K. 1MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of ARSENIC TRIOXIDE S.K. 1 mg/ml contains 1 mg of arsenic trioxide.

Each vial of 10 ml contains 10 mg of arsenic trioxide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear colourless aqueous solution.

The pH of the solution is 6.0-8.0 and the osmolality of the solution is 58 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARSENIC TRIOXIDE S.K. 1MG/ML is indicated for induction of remission, and consolidation in adult patients with:

• Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 103/µl) in combination with all-*trans*-retinoic acid (ATRA).

• Relapsed/refractory acute promyelocytic leukaemia (APL) (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.

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

4.2 Posology and method of administration

ARSENIC TRIOXIDE S.K. 1MG/ML must be administered under the supervision of a physician who is experienced in the management of acute leukaemia, and the special monitoring procedures described in section 4.4 must be followed.

Posology

The same dose is recommended for adults and elderly.

Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL)

Induction treatment schedule

ARSENIC TRIOXIDE S.K. 1MG/ML 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.

Consolidation schedule

ARSENIC TRIOXIDE S.K. 1MG/ML 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.

Relapsed/refractory acute promyelocytic leukaemia (APL)

Induction treatment schedule

ARSENIC TRIOXIDE S.K. 1MG/ML 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.

Consolidation schedule

Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. ARSENIC TRIOXIDE S.K. 1MG/ML 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.

Dose delay, modification and reinitiation

Treatment with ARSENIC TRIOXIDE S.K. 1MG/ML must be temporarily interrupted before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to ARSENIC TRIOXIDE S.K. 1MG/ML treatment. Patients who experience such reactions that are considered ARSENIC TRIOXIDE S.K. 1MG/ML related must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50 % of the preceding daily dose. If the toxic event does not recur within 7 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100 % of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.

For ECG, electrolytes abnormalities and hepatotoxicity see section 4.4.

Special populations

Patients with hepatic impairment

Since no data are available across all hepatic impairment groups and hepatotoxic effects may occur

during the treatment with ARSENIC TRIOXIDE S.K. 1MG/ML, caution is advised in the use of ARSENIC TRIOXIDE S.K. 1MG/ML in patients with hepatic impairment (see sections 4.4 and 4.8).

Patients with renal impairment

Since no data are available across all renal impairment groups, caution is advised in the use of ARSENIC TRIOXIDE S.K. 1MG/ML in patients with renal impairment.

Paediatric population

ARSENIC TRIOXIDE S.K. 1MG/ML is not indicated in children and adolescents below 18 years old.

Method of administration

ARSENIC TRIOXIDE S.K. 1MG/ML must be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if vasomotor reactions are observed. A central venous catheter is not required. Patients must be hospitalised at the beginning of treatment due to symptoms of disease and to ensure adequate monitoring.

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
ARSENIC TRIOXIDE S.K. 1MG/ML is contraindicated in pregnancy or when there is a possibility of pregnancy (see Section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Clinically unstable APL patients are especially at risk and will require more frequent monitoring of electrolyte and glycaemia levels as well as more frequent haematologic, hepatic, renal and coagulation parameter tests.

Leukocyte activation syndrome (APL differentiation syndrome)

27% of patients with APL, in the relapsed/refractory setting, treated with arsenic trioxide have experienced symptoms similar to a syndrome called the retinoic-acid-acute promyelocytic leukaemia (RA-APL) or APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal.

In newly diagnosed APL patients treated with arsenic trioxide and all-*trans*-retinoic acid (ATRA), APL differentiation syndrome was observed in 19 % including 5 severe cases. At the first signs that could suggest the syndrome (unexplained fever, dyspnoea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), treatment with ARSENIC TRIOXIDE S.K. 1MG/ML must be temporarily discontinued and high-dose steroids (dexamethasone 10 mg intravenously twice a day) must be immediately initiated, irrespective of the leukocyte count and continued for at least 3 days or longer until signs and symptoms have abated. If clinically justified/required, concomitant diuretic therapy is also recommended. The majority of patients do not require permanent termination of ARSENIC TRIOXIDE S.K. 1MG/ML therapy during treatment of the APL differentiation syndrome. As soon as signs and symptoms have subsided, treatment with ARSENIC TRIOXIDE S.K. 1MG/ML can be resumed at 50 % of the previous dose during the first 7 days. Thereafter, in the absence of worsening of the previous toxicity, ARSENIC TRIOXIDE S.K. 1MG/ML might be resumed at full dosage. In the case of the reappearance of symptoms ARSENIC TRIOXIDE S.K. 1MG/ML should be reduced to the previous dosage. In order to prevent the development of the APL differentiation syndrome during induction treatment, prednisone (0.5 mg/kg body weight per day throughout induction treatment) may be administered from day 1 of ARSENIC TRIOXIDE S.K. 1MG/ML application to the end of induction therapy in APL patients. It is recommended that chemotherapy not be added to treatment with steroids since there is no experience with administration of both steroids and chemotherapy during treatment of the leukocyte

activation syndrome due to ARSENIC TRIOXIDE S.K. 1MG/ML. Post-marketing experience suggests that a similar syndrome may occur in patients with other types of malignancy. Monitoring and management for these patients should be as described above.

Electrocardiogram (ECG) abnormalities

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. Previous treatment with anthracyclines may increase the risk of QT prolongation. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging medicinal products (such as class Ia and III antiarrythmics (e.g. quinidine, amiodarone, sotalol, dofetilide), antipsychotics (e.g. thioridazine), antidepressants (e.g. amitriptyline), some macrolides (e.g. erythromycin), some antihistamines (e.g. terfenadine and astemizole), some quinolone antibiotics (e.g. sparfloxacin), and other individual medicinal products known to increase QT interval (e.g. cisapride), a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, amphotericin B or other conditions that result in hypokalaemia or hypomagnesaemia. In clinical trials, in the relapsed/refractory setting, 40 % of patients treated with ARSENIC TRIOXIDE experienced at least one QT corrected (QTc) interval prolongation greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after ARSENIC TRIOXIDE infusion, and then returned to baseline by the end of 8 weeks after ARSENIC TRIOXIDE infusion. One patient (receiving multiple, concomitant medicinal products, including amphotericin B) had asymptomatic torsade de pointes during induction therapy for relapsed APL with arsenic trioxide. In newly diagnosed APL patients 15.6 % showed QTc prolongation with arsenic trioxide in combination with ATRA (see section 4.8). 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.

ECG and electrolyte monitoring recommendations

Prior to initiating therapy with ARSENIC TRIOXIDE S.K. 1MG/ML, 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, 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). 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 ARSENIC TRIOXIDE S.K. 1MG/ML. During therapy with ARSENIC TRIOXIDE S.K. 1MG/ML, 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 ARSENIC TRIOXIDE S.K. 1MG/ML therapy must be considered. If syncope, rapid or irregular heartbeat develops, the patient must be hospitalised and monitored continuously, serum electrolytes must be assessed, ARSENIC TRIOXIDE S.K. 1MG/ML 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 ARSENIC TRIOXIDE S.K. 1MG/ML 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 arsenic trioxide on the QTc interval during the infusion. Electrocardiograms must be obtained twice weekly, and more frequently for clinically unstable patients, during induction and consolidation.

Hepatotoxicity (grade 3 or greater)

In newly diagnosed patients with low to intermediate risk APL 63.2 % developed grade 3 or 4 hepatic toxic effects during induction or consolidation treatment with arsenic trioxide in combination with ATRA (see section 4.8). However, toxic effects resolved with temporary discontinuation of either arsenic trioxide, ATRA or both. Treatment with ARSENIC TRIOXIDE S.K. 1MG/ML must be discontinued before the scheduled end of therapy at any time that a hepatotoxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed. As soon as bilirubin and/or SGOT and/or alkaline phosphatase are decreased to below 4 times the normal upper level, treatment with ARSENIC TRIOXIDE S.K. 1MG/ML should be resumed at 50 % of the previous dose during the first 7 days. Thereafter, in absence of worsening of the previous toxicity, ARSENIC TRIOXIDE S.K. 1MG/ML should be resumed at full dosage. In case of reappearance of hepatotoxicity, ARSENIC TRIOXIDE S.K. 1MG/ML must be permanently discontinued.

Dose delay and modification

Treatment with ARSENIC TRIOXIDE S.K. 1MG/ML must be temporarily interrupted before the scheduled end of therapy at any time that a toxicity grade 3 or greater on the National Cancer Institute Common Toxicity Criteria is observed and judged to be possibly related to ARSENIC TRIOXIDE S.K. 1MG/ML treatment. (see section 4.2).

Laboratory tests

The patient's electrolyte and glycaemia levels, as well as haematologic, hepatic, renal and coagulation parameter tests must be monitored at least twice weekly, and more frequently for clinically unstable patients during the induction phase and at least weekly during the consolidation phase.

Patients with renal impairment

Since no data are available across all renal impairment groups, caution is advised in the use of ARSENIC TRIOXIDE S.K. 1MG/ML in patients with renal impairment. The experience in patients with severe renal impairment is insufficient to determine if dose adjustment is required.

The use of ARSENIC TRIOXIDE in patients on dialysis has not been studied.

Patients with hepatic impairment

Since no data are available across all hepatic impairment groups and hepatotoxic effects may occur during the treatment with arsenic trioxide caution is advised in the use of ARSENIC TRIOXIDE S.K. 1MG/ML in patients with hepatic impairment (see section 4.4 on hepatotoxicity and section 4.8). The experience in patients with severe hepatic impairment is insufficient to determine if dose adjustment is required.

Elderly

There is limited clinical data on the use of ARSENIC TRIOXIDE in the elderly population. Caution is needed in these patients.

Hyperleukocytosis

Treatment with arsenic trioxide has been associated with the development of hyperleukocytosis ($\geq$ 10 x 103/ μ l) in some relapsed/refractory APL patients. There did not appear to be a relationship between baseline white blood cell (WBC) counts and development of hyperleukocytosis nor did there appear to be a correlation between baseline WBC count and peak WBC counts. Hyperleukocytosis was never treated with additional chemotherapy and resolved on continuation of ARSENIC TRIOXIDE. WBC counts during consolidation were not as high as during induction treatment and were < 10 x 103/ μ l, except in one patient who had a WBC count of 22 x 103/ μ l during consolidation. Twenty relapsed/refractory APL patients (50 %) experienced leukocytosis; however, in all these patients, the WBC count was declining or had normalized by the time of bone marrow remission and cytotoxic chemotherapy or leukopheresis was not required. In newly diagnosed patients with low to intermediate risk APL leukocytosis developed during induction therapy in 35 of 74 (47 %) patients (see section 4.8). However, all cases were successfully managed with hydroxyurea therapy.

In newly diagnosed and relapsed/refractory APL patients who develop sustained leukocytosis after initiation of therapy, hydroxyurea should be administered. Hydroxyurea should be continued at a given dose to keep the white blood cell count $\leq$ 10 x 103/ μ l and subsequently tapered.

Table 1 Recommendation for initiation of hydroxyurea

WBC	Hydroxyurea
10–50 x 10^3/µl	500 mg four times a day
> 50 x 10^3/µl	1000 mg four times a day

Development of second primary malignancies

The active ingredient of ARSENIC TRIOXIDE S.K. 1MG/ML, arsenic trioxide, is a human carcinogen. Monitor patients for the development of second primary malignancies.

Encephalopathy

Cases of encephalopathy were reported with treatment with arsenic trioxide. Wernicke encephalopathy after arsenic trioxide treatment was reported in patients with vitamin B1 deficiency. Patients at risk of B1 deficiency should be closely monitored for signs and symptoms of encephalopathy after arsenic trioxide initiation. Some cases recovered with vitamin B1 supplementation.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal assessments of pharmacokinetic interactions between ARSENIC TRIOXIDE and other therapeutic medicinal products have been conducted.

Medicinal products known to cause QT/QTc interval prolongation, hypokalaemia or hypomagnesaemia

QT/QTc prolongation is expected during treatment with arsenic trioxide, and 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 ARSENIC TRIOXIDE S.K. 1MG/ML 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. Additional information about QT prolonging medicinal agents, is provided in section 4.4.

Medicinal products known to cause hepatotoxic effects

Hepatotoxic effects may occur during the treatment with arsenic trioxide, caution is advised when ARSENIC TRIOXIDE S.K. 1MG/ML is co-administered with other medicinal products known to cause hepatotoxic effects (see sections 4.4 and 4.8).

Other antileukaemic medicinal products

The influence of ARSENIC TRIOXIDE S.K. 1MG/ML on the efficacy of other antileukaemic medicinal products is unknown.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Due to the genotoxic risk of arsenic compounds (see section 5.3), women of childbearing potential must use effective contraceptive measures during treatment with ARSENIC TRIOXIDE S.K. 1MG/ML and for 6 months following completion of treatment.

Men should use effective contraceptive measures and be advised to not father a child while receiving ARSENIC TRIOXIDE S.K. 1MG/ML and for 3 months following completion of treatment.

Pregnancy

Arsenic trioxide has been shown to be embryotoxic and teratogenic in animal studies (see section 5.3). There are no studies in pregnant women using ARSENIC TRIOXIDE. If this medicinal product is used during pregnancy or if the patient becomes pregnant while taking this product, the patient must be informed of the potential harm to the foetus.

Breast-feeding

Arsenic is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants and children from ARSENIC TRIOXIDE S.K. 1MG/ML, breastfeeding must be discontinued prior to and throughout administration and for two weeks after the last dose.

Fertility

No clinical or non-clinical fertility studies have been conducted with ARSENIC TRIOXIDE.

4.7 Effects on ability to drive and use machines

ARSENIC TRIOXIDE S.K. 1MG/ML has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Related adverse reactions of CTC grade 3 and 4 occurred in 37 % of relapsed/refractory APL patients in clinical trials. The most commonly reported reactions were hyperglycaemia, hypokalaemia, neutropenia, and increased alanine amino transferase (ALT). Leukocytosis occurred in 50 % of patients with relapsed/refractory APL, as determined by haematology assessments.

Serious adverse reactions were common (1-10 %) and not unexpected in the relapsed/refractory population. Those serious adverse reactions attributed to arsenic trioxide included APL differentiation syndrome (3), leukocytosis (3), prolonged QT interval (4, 1 with torsade de pointes), atrial fibrillation/atrial flutter (1), hyperglycaemia (2) and a variety of serious adverse reactions related to haemorrhage, infections, pain, diarrhoea, nausea.

In general, treatment-emergent adverse events tended to decrease over time, in relapsed/refractory APL patients perhaps accounted for by amelioration of the underlying disease process. Patients tended to tolerate consolidation and maintenance treatment with less toxicity than in induction. This is probably due to the confounding of adverse events by the uncontrolled disease process early on in the treatment course and the myriad concomitant medicinal products required to control symptoms and morbidity.

In a phase 3, multicentre, non-inferiority trial comparing all-*trans*-retinoic acid (ATRA) plus chemotherapy with ATRA plus arsenic trioxide in newly diagnosed low-to-intermediate risk APL patients (Study APL0406; see also section 5.1), serious adverse reactions including hepatic toxicity, thrombocytopenia, neutropenia and QTc prolongation were observed in patients treated with arsenic trioxide.

Tabulated list of adverse reactions

The following undesirable effects have been reported in the APL0406 study in newly diagnosed patients and in clinical trials and/or post-marketing experience in relapsed/refractory APL patients. Undesirable effects are listed in table 2 below as MedDRA preferred term by system organ class and frequencies observed during ARSENIC TRIOXIDE clinical trials in 52 patients with refractory/relapsed APL. Frequencies are defined as: (very common $\geq$ 1/10), (common $\geq$ 1/100 to < 1/10), (uncommon $\geq$ 1/1,000 to < 1/100), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2

	All grades	Grades ≥ 3
Infections and infestations		
Herpes zoster	Common	Not known
Sepsis	Not known	Not known
Pneumonia	Not known	Not known
Blood and lymphatic system disorders		
Febrile neutropenia	Common	Common
Leukocytosis	Common	Common
Neutropenia	Common	Common
Pancytopenia	Common	Common
Thrombocytopenia	Common	Common
Anaemia	Common	Not known
Leukopenia	Not known	Not known
Lymphopenia	Not known	Not known
Metabolism and nutrition disorders		
Hyperglycaemia	Very Common	Very Common
Hypokalaemia	Very Common	Very Common
Hypomagnesaemia	Very Common	Common
Hypernatraemia	Common	Common
Ketoacidosis	Common	Common
Hypermagnesaemia	Common	Not known
Dehydration	Not known	Not known
Fluid retention	Not known	Not known
Psychiatric disorders		
Confusional state	Not known	Not known
Nervous system disorders		
Paraesthesia	Very Common	Common
Dizziness	Very Common	Not known
Headache	Very Common	Not known
Convulsion	Common	Not known
Encephalopathy, Wernicke encephalopathy	Not known	Not known
Eye disorders		
Vision blurred	Common	Not known
Cardiac disorders		
Tachycardia	Very Common	Common
Pericardial effusion	Common	Common
Ventricular extrasystoles	Common	Not known
Cardiac failure	Not known	Not known
Ventricular tachycardia	Not known	Not known
Vascular disorders		
Vasculitis	Common	Common
Hypotension	Common	Not known
Respiratory, thoracic and mediastinal disorders		
Differentiation syndrome	Very Common	Very Common
Dyspnoea	Very Common	Common
Hypoxia	Common	Common
Pleural effusion	Common	Common

Pleuritic pain	Common	Common
Pulmonary alveolar haemorrhage	Common	Common
Pneumonitis	Not known	Not known
Gastrointestinal disorders		
Diarrhoea	Very Common	Common
Vomiting	Very Common	Not known
Nausea	Very Common	Not known
Abdominal pain	Common	Common
Skin and subcutaneous tissue disorders		
Pruritus	Very Common	Not known
Rash	Very Common	Not known
Erythema	Common	Common
Face oedema	Common	Not known
Musculoskeletal and connective tissue disorders		
Myalgia	Very Common	Common
Arthralgia	Common	Common
Bone pain	Common	Common
Renal and urinary disorders		
Renal failure	Common	Not known
General disorders and administration site conditions		
Pyrexia	Very Common	Common
Pain	Very Common	Common
Fatigue	Very Common	Not known
Oedema	Very Common	Not known
Chest pain	Common	Common
Chills	Common	Not known
Investigations		
Alanine amino transferase increased	Very Common	Common
Aspartate amino transferase increased	Very Common	Common
Electrocardiogram QT prolonged	Very Common	Common
Hyperbilirubinaemia	Common	Common
Blood creatinine increased	Common	Not known
Weight increased	Common	Not known
Gamma-glutamyltransferase increased*	Not known*	Not known*

**In the CALGB study C9710, 2 cases of grade ≥3 increased GGT were reported out of the 200 patients who received ARSENIC TRIOXIDE consolidation cycles (cycle 1 and cycle 2) versus none in the control arm.*

Description of selected adverse reactions

Differentiation syndrome

During ARSENIC TRIOXIDE treatment, 14 of the 52 patients in the APL studies in the relapsed setting had one or more symptoms of APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis (see section 4.4). Twenty-seven patients had leukocytosis (WBC ≥ 10 x 103/µl) during induction, 4 of whom had values above 100,000/µl.

Baseline white blood cell (WBC) counts did not correlate with development of leukocytosis on study, and WBC counts during consolidation therapy were not as high as during induction. In these studies, leukocytosis was not treated with chemotherapeutic medicinal products. Medicinal products that are used to lower the white blood cell count often exacerbate the toxicities associated with leukocytosis, and no standard approach has proven effective. One patient treated under a compassionate use program died from cerebral infarct due to leukocytosis, following treatment with chemotherapeutic medicinal products to lower WBC count. Observation is the recommended approach with intervention only in selected cases.

Mortality in the pivotal studies in the relapsed setting from disseminated intravascular coagulation (DIC) associated haemorrhage was very common (> 10 %), which is consistent with the early mortality reported in the literature.

In newly diagnosed patients with low to intermediate risk APL, differentiation syndrome was observed in 19 % including 5 severe cases.

In post marketing experience, a differentiation syndrome, like retinoic acid syndrome, has also been reported for the treatment of malignancies other than APL with ARSENIC TRIOXIDE.

QT interval prolongation

Arsenic trioxide can cause QT interval prolongation (see section 4.4). QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging medicinal products, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalaemia or hypomagnesaemia. One patient (receiving multiple, concomitant medicinal products, including amphotericin B) had asymptomatic torsade de pointes during induction therapy for relapsed APL with arsenic trioxide. She went onto consolidation without further evidence of QT prolongation.

In newly diagnosed patients, with low to intermediate risk APL, QTc prolongation was observed in 15.6 %. In one patient induction treatment was terminated because of severe prolongation of the QTc interval and electrolyte abnormalities on day 3.

Peripheral neuropathy

Peripheral neuropathy, characterised by paraesthesia/dysaesthesia , is a common and well-known effect of environmental arsenic. Only 2 relapsed/refractory APL patients discontinued treatment early due to this adverse event and one went on to receive additional ARSENIC TRIOXIDE on a subsequent protocol. Forty-four per cent of relapsed/refractory APL patients experienced symptoms that could be associated with neuropathy; most were mild to moderate and were reversible upon cessation of treatment with ARSENIC TRIOXIDE.

Hepatotoxicity (grade 3-4)

In newly diagnosed patients with low to intermediate risk APL 63.2 % developed grade 3 or 4 hepatic toxic effects during induction or consolidation treatment with ARSENIC TRIOXIDE in combination with ATRA. However, toxic effects resolved with temporary discontinuation of either ARSENIC TRIOXIDE, ATRA or both (see section 4.4).

Haematological and gastrointestinal toxicity

In newly diagnosed patients with low to intermediate risk APL, gastrointestinal toxicity, grade 3-4 neutropenia and grade 3 or 4 thrombocytopenia occurred, however these were 2.2 times less frequent in patients treated with ARSENIC TRIOXIDE in combination with ATRA compared to patients treated with ATRA + chemotherapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

If symptoms suggestive of serious acute arsenic toxicity (*e.g*. convulsions, muscle weakness and confusion) appear, ARSENIC TRIOXIDE S.K. 1MG/ML must be immediately discontinued and chelating therapy with penicillamine at a daily dose $\leq$ 1 g per day may be considered. The duration of treatment with penicillamine must be evaluated taking into account the urinary arsenic laboratory values. For patients who cannot take oral medicinal product, dimercaprol administered at a dose of 3 mg/kg intramuscularly every 4 hours until any immediately life-threatening toxicity has subsided may be considered. Thereafter, penicillamine at a daily dose $\leq$ 1 g per day may be given. In the presence of coagulopathy, the oral administration of the chelating agent Dimercaptosuccinic Acid Succimer (DCI) 10 mg/kg or 350 mg/m2 every 8 hours during 5 days and then every 12 hours during 2 weeks is recommended. For patients with severe, acute arsenic overdose, dialysis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX27

Mechanism 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/RAR alpha).

Clinical efficacy and safety

Newly diagnosed non high risk APL patients

ARSENIC TRIOXIDE has been investigated in 77 newly diagnosed patients with low to intermediate risk APL, in a controlled, randomized, non-inferiority Phase 3 clinical study comparing the efficacy and safety of ARSENIC TRIOXIDE combined with all-*trans*-retinoic acid (ATRA) with those of ATRA + chemotherapy (e.g., idarubicin and mitoxantrone) (Study APL0406). Patients with newly diagnosed APL confirmed by the presence of t(15; 17) or PML-RAR α by RT-PCR or micro speckled PML nuclear distribution in leukaemic cells were included. No data are available on patient with variant translocations like t(11;17) (PLZF/RAR α). Patients with significant arrhythmias, EKG abnormalities (congenital long QT syndrome, history or presence of significant ventricular or

atrial tachyarrhythmia, clinically significant resting bradycardia (< 50 beats per minute), QTc > 450 msec on screening EKG, right bundle branch block plus left anterior hemiblock, bifascicular block) or neuropathy were excluded from the study. Patients in the ATRA + ARSENIC TRIOXIDE treatment group received oral ATRA at 45 mg/m2 daily and IV ARSENIC TRIOXIDE at 0.15 mg/kg daily until CR. During consolidation, ATRA was given at the same dose for periods of 2 weeks on and 2 weeks off for a total of 7 courses, and ARSENIC TRIOXIDE was given at the same dose 5 days per week, 4 weeks on and 4 weeks off, for a total of 4 courses. Patients in the ATRA + chemotherapy treatment group received IV idarubicin at 12 mg/m2 on days 2, 4, 6, and 8 and oral ATRA at 45 mg/m2 daily until CR. During consolidation, patients received idarubicin at 5 mg/m2 on days 1 to 4 and ATRA at 45 mg/m2 daily for 15 days, then IV mitoxantrone at 10 mg/m2 on days 1 to 5 and ATRA again at 45 mg/m2 daily for 15 days, and finally a single dose of idarubicin at 12 mg/m2 and ATRA at 45 mg/m2 daily for 15 days. Each course of consolidation was initiated at haematological recovery from the previous course defined as absolute neutrophil count > 1.5 x 109/l and platelets > 100 x 109/l. Patients in the ATRA + chemotherapy treatment group also received maintenance treatment for up to 2 years, consisting of oral 6-mercaptopurine at 50 mg/m2 daily, intramuscular methotrexate at 15 mg/m2 weekly, and ATRA at 45 mg/m2 daily for 15 days every 3 months.

The key efficacy results are summarised in table 3 below:

Table 3

Endpoint	**ATRA + ARSENIC TRIOXIDE (n = 77) [%]**	**ATRA + Chemotherapy (n = 79) [%]**	**Confidence interval (CI)**	**P-value**
2-Year event-free survival (EFS)	97	86	95 % CI for the difference, 2-22 percentage points	p < 0.001 for non-inferiority p = 0.02 for superiority of ATRA + ARSENIC TRIOXIDE
Haematologic complete remission (HCR)	100	95		p = 0.12
2-Year overall survival (OS)	99	91		p = 0.02
2-Year disease-free survival (DFS)	97	90		p = 0.11
2-Year cumulative incidence of relapse (CIR)	1	6		p = 0.24

APL = acute promyelocytic leukaemia; ATRA = all-*trans*-retinoic acid

Relapsed/refractory APL

ARSENIC TRIOXIDE has been investigated in 52 APL patients, previously treated with an anthracycline and a retinoid regimen, in two open-label, single-arm, non-comparative studies. One was a single investigator clinical study (n=12) and the other was a multicentre, 9-institution study (n=40). Patients in the first study received a median dose of 0.16 mg/kg/day of ARSENIC TRIOXIDE (range 0.06 to 0.20 mg/kg/day) and patients in the multicentre study received a fixed dose of 0.15 mg/kg/day. ARSENIC TRIOXIDE was administered intravenously over 1 to 2 hours until the bone marrow was free of leukaemic cells, up to a maximum of 60 days. Patients with complete remission received consolidation therapy with ARSENIC TRIOXIDE for 25 additional doses over a 5 week period. Consolidation therapy began 6 weeks (range, 3-8) after induction in the single institution study and 4 weeks (range, 3-6) in the multicentre study. Complete remission (CR) was defined as the absence of visible leukaemic cells in the bone marrow and peripheral recovery of platelets and white blood cells.

Patients in the single centre study had relapsed following 1-6 prior therapy regimens and 2 patients had relapsed following stem cell transplantation. Patients in the multicentre study had relapsed following 1-4 prior therapy regimens and 5 patients had relapsed following stem cell transplantation. The median age in the single centre study was 33 years (age range 9 to 75). The median age in the multicentre study was 40 years (age range 5 to 73).

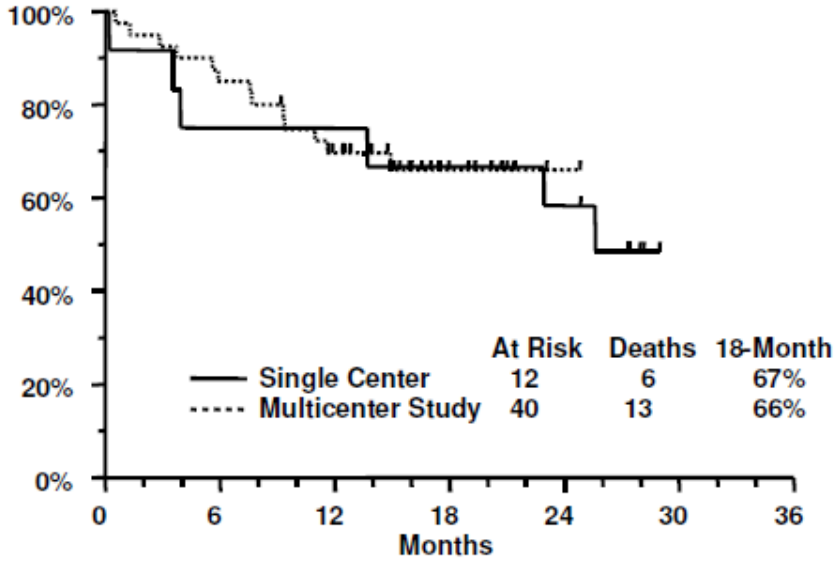
The results are summarised in the table 4 below.

Table 4

	Single centre trial N=12	**Multicentre trial N=40**
ARSENIC TRIOXIDE dose, mg/kg/day (median, range)	0.16 (0.06 – 0.20)	0.15
Complete remission	11 (92 %)	34 (85 %)
Time to bone marrow remission (median)	32 days	35 days
Time to CR (median)	54 days	59 days
18-Month survival	67 %	66 %

The single institution study included 2 paediatric patients (< 18 years old), both of whom achieved CR. The multicentre trial included 5 paediatric patients (< 18 years old), 3 of whom achieved CR. No children of less than 5 years of age were treated.

In a follow-up treatment after consolidation, 7 patients in the single institution study and 18 patients in the multicentre study received further maintenance therapy with ARSENIC TRIOXIDE. Three patients from the single institution study and 15 patients from the multicentre study had stem cell transplants after completing ARSENIC TRIOXIDE . The Kaplan-Meier median CR duration for the single institution study is 14 months and has not been reached for the multicentre study. At last follow-up, 6 of 12 patients in the single institution study were alive with a median follow-up time of 28 months (range 25 to 29). In the multicentre study 27 of 40 patients were alive with a median follow-up time of 16 months (range 9 to 25). Kaplan-Meier estimates of 18-month survival for each study are shown below.



Cytogenetic confirmation of conversion to a normal genotype and reverse transcriptase – polymerase chain reaction (RT-PCR) detection of PML/RARα conversion to normal are shown in table 5 below.

Cytogenetics after ARSENIC TRIOXIDE therapy

Table 5

	Single centre pilot trial N with CR = 11	**Multicentre trial N with CR = 34**
Conventional Cytogenetics [t(15;17)]		
Absent	8 (73 %)	31 (91 %)
Present	1 (9 %)	0 %
Not evaluable	2 (18 %)	3 (9 %)
RT-PCR for PML/ RARα		
Negative	8 (73 %)	27 (79 %)
Positive	3 (27 %)	4 (12 %)
Not evaluable	0	3 (9 %)

Responses were seen across all age groups tested, ranging from 6 to 75 years. The response rate was similar for both genders. There is no experience on the effect of ARSENIC TRIOXIDE on the variant APL containing the t(11;17) and t(5;17) chromosomal translocations.

5.2 Pharmacokinetic properties

The inorganic, lyophilized form of arsenic trioxide, when placed into solution, immediately forms the hydrolysis product arsenious acid (As^{III}). As^{III} is the pharmacologically active species of arsenic trioxide.

Distribution

The volume of distribution (Vd) for AsIII is large (> 400 l) indicating significant distribution into the tissues with negligible protein binding. Vd is also weight dependent, increasing with increasing body weight. Total arsenic accumulates mainly in the liver, kidney, and heart and, to a lesser extent, in the lung, hair, and nails.

Biotransformation

The metabolism of arsenic trioxide involves oxidation of arsenious acid (AsIII), the active species of arsenic trioxide, to arsenic acid (AsV), as well as oxidative methylation to monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV) by methyltransferases, primarily in the liver. The pentavalent metabolites, MMAV and DMAV, are slow to appear in plasma (approximately 10-24 hours after first administration of arsenic trioxide), but due to their longer half-life, accumulate more upon multiple dosing than does AsIII. The extent of accumulation of these metabolites is dependent on the dosing regimen. Approximate accumulation ranged from 1.4- to 8-fold following multiple as compared to single dose administration. AsV is present in plasma only at relatively low levels.

In vitro enzymatic studies with human liver microsomes revealed that arsenic trioxide has no inhibitory activity on substrates of the major cytochrome P450 enzymes such as 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A9/11. Substances that are substrates for these P450 enzymes are not expected to interact with ARSENIC TRIOXIDE.

Elimination

Approximately 15 % of the administered ARSENIC TRIOXIDE dose is excreted in the urine as unchanged As^{III}. The methylated metabolites of As^{III} (MMAV, DMAV) are primarily excreted in the urine. The plasma concentration of As^{III} declines from peak plasma concentration in a biphasic manner with a mean terminal elimination half-life of 10 to 14 hours. The total clearance of As^{III} over the single-dose range of 7-32 mg (administered as 0.15 mg/kg) is 49 l/h and the renal clearance is 9 l/h. Clearance is not dependent on the weight of the subject or the dose administered over the dose range studied. The mean estimated terminal elimination half-lives of the metabolites MMAV and DMAV are 32 hours and 70 hours, respectively.

Renal impairment

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 (see section 4.4).

Systemic exposure to MMAV and DMAV tended to be larger in patients with renal impairment; the clinical consequence of this is unknown but no increased toxicity was noted.

Hepatic impairment

Pharmacokinetic data from patients with hepatocellular carcinoma having mild to moderate hepatic impairment indicate that As^{III} or AsV do not accumulate following twice-weekly infusions. No clear trend toward an increase in systemic exposure to As^{III}, AsV, MMAV or DMAV was observed with decreasing level of hepatic function as assessed by dose-normalized (per mg dose) AUC.

Linearity/non-linearity

In the total single dose range of 7 to 32 mg (administered as 0.15 mg/kg), systemic exposure (AUC) appears to be linear. The decline from peak plasma concentration of As^{III} occurs in a biphasic manner and is characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. After administration at 0.15 mg/kg on a daily (n=6) or twice-weekly (n=3) regimen, an approximate 2-fold accumulation of As^{III} was observed as compared to a single infusion. This accumulation was slightly more than expected based on single-dose results.

5.3 Preclinical safety data

Limited reproductive toxicity studies of arsenic trioxide in animals indicate embryotoxicity and teratogenicity (neural tube defects, anophthalmia and microphthalmia) at administration of 1-10 times the recommended clinical dose (mg/m2). Fertility studies have not been conducted with ARSENIC TRIOXIDE.

Arsenic compounds induce chromosomal aberrations and morphological transformations of mammalian cells *in vitro* and *in vivo*. No formal carcinogenicity studies of arsenic trioxide have been performed. However, arsenic trioxide and other inorganic arsenic compounds are recognised as human carcinogens.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
The expiry date of the product is indicated on the packaging materials.

After first opening
Once opened the product should be used immediately.

After dilution
Following its withdrawal from the vial, and immediate dilution with 100 to 250 ml of glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection, ARSENIC TRIOXIDE S.K. 1MG/ML was demonstrated to be chemically and physically stable for 24 hours at 15-25°C and 48 hours at 2-8 °C.

From a microbiological point of view, the product should be used immediately. If

not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30^0C. Do not freeze.

For storage conditions after dilution of the medicinal products, see section 6.3.

6.5 Nature and contents of container

10 ml clear Type I glass vial with a bromobutyl rubber stopper grey (FluroTec coated) and sealed with an aluminium flip-off cap with polypropylene disk.

Each carton contains 10 vials. Each vial contains 10 ml of concentrate solution. **6.6 Special precautions for disposal and other handling**

Preparation of ARSENIC TRIOXIDE S.K. 1MG/ML

Aseptic technique must be strictly observed throughout handling of ARSENIC TRIOXIDE S.K. 1MG/ML since no preservative is present.

ARSENIC TRIOXIDE S.K. 1MG/ML must be diluted with 100 to 250 ml of glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection immediately after withdrawal from the vial. It is for single use only, and any unused portions of each vial must be discarded properly. Do not save any

unused portions for later administration.

ARSENIC TRIOXIDE S.K. 1MG/ML must not be mixed with or concomitantly administered in the same intravenous line with other medicinal products.

The diluted solution must be clear and colourless. All parenteral solutions must be inspected visually for

particulate matter and discoloration prior to administration. Do not use the preparation if foreign

particulate matter is present.

Procedure for proper disposal

Any unused medicinal product, any items that come into contact with the product or waste material

must be disposed of in accordance with local requirements.

7. LICENCE HOLDER AND MANUFACTURER

Licence holder:

K.S.Kim International (SK-PHARMA) Ltd.

94 YIGAL ALON STR., TEL-AVIV-YAFO, 6789139, Israel.

Manufacturer:

Oncomed Manufacturing a.s.
Karásek 2229/1b, Budova 02, Řečkovice, 621 00 Brno, Czechia.

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167-36-36741-99

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