25 juli, 2017

Kommunikation till hälso- och sjukvårdspersonal

Restsituation för Trisenox® (arseniktrioxid) 1 mg/ml koncentrat till infusionsvätska: ersättning med importerat arseniktrioxid 1 mg/ml för injektion

Bästa förskrivare,

Teva B.V. (innehavare av godkännande för försäljning av Trisenox) och Teva Sweden AB (ansvarigt marknadsbolag i Sverige) i överenskommelse med Europeiska läkemedelsmyndigheten (EMA) och Läkemedelsverket, vill informera dig om följande:

Sammanfattning

- **Problem med tillverkning av Trisenox förväntas leda till restsituation på den europeiska marknaden vid mitten/slutet av augusti 2017, men restsituationen har redan uppstått i Sverige. Säkerhet och effekt av produkten som för närvarande finns på marknaden är inte påverkade av tillverkningsproblemen.**
- **I syfte att säkerställa kontinuiteten av leverans av arseniktrioxid till EU, har Teva beslutat importera en likvärdig produkt från Australien som innehåller 1 mg/ml arseniktrioxid (Phenasen från Phebra Pty Ltd).**
- **Phenasen och Trisenox innehåller samma aktiva substans, arseniktrioxid, i samma totalkoncentration: 10 mg arseniktrioxid i 10 ml. Trisenox är tillgänglig i en ampull, medan Phenasen är tillgänglig i en injektionsflaska.**

Bakgrund

Trisenox (arseniktrioxid) är avsett för induktion av remission och konsolidering hos vuxna patienter med:

- Nydiagnosticerad akut promyeloisk leukemi (APL) med låg till intermediär risk (antal vita blodkroppar $\leq 10 \times 10^3/\mu l$) i kombination med all-*trans*-retinoidsyra (ATRA),
- Recidiverande/behandlingsresistent akut promyeloisk leukemi (APL), (tidigare behandling ska ha innefattat en retinoid samt kemoterapi),
  som karakteriseras av en t(15;17) translokation och/eller förekomst av genen Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alfa).

Teva bytte nyligen tillverkare av Trisenox, vilket godkändes i EU den 5 maj 2017. Det har förekommit vissa problem med tillverkningen hos den nya tillverkaren, som för närvarande arbetar hårt för att komma tillrätta med situationen. Vid en visuell undersökning av ampuller innehållande vissa tillverkningssatser av Trisenox var lösningen grumlig istället för klar. En utredning pågår för att identifiera grundorsaken och vidta nödvändiga korrigerande och förebyggande åtgärder. Inga

tillverkningssatser från den nya tillverkaren kommer att frisläppas till den europeiska marknaden förrän utredningen slutförts med ett fullgott resultat. De Trisenox-ampuller som för närvarande är ute på marknaden är inte påverkade av tillverkningsproblemen.

Den europeiska marknaden förses för närvarande med Trisenox-ampuller från den tidigare tillverkaren. Detta lager kommer emellertid ta slut och trots att Teva gör stora insatser för att fördela lagret över den europeiska marknaden, förväntas lagren vara slut vid mitten/slutet av augusti 2017.

I syfte att säkerställa kontinuiteten av leverans av arseniktrioxid till EU, har Teva beslutat importera en likvärdig produkt från Australien som innehåller 1 mg/ml arseniktrioxid (Phenasen från Phebra Pty Ltd). I Sverige kommer denna produkt finnas tillgänglig genom licensförskrivning.

Både Phenasen och Trisenox innehåller samma aktiva substans, arseniktrioxid, i samma totalkoncentration: 10 mg arseniktrioxid i 10 ml. Vänligen notera att medan Trisenox är tillgänglig i en ampull, är Phenasen tillgänglig i en injektionsflaska.

Kontaktinformation på företaget
Om du har några ytterligare frågor om produkttillgänglighet eller beställning av Trisenox, vänligen kontakta Tevas svenska marknadsbolag:

Teva Sweden AB
Box 1070
251 10 Helsingborg
Tel: 042-12 11 00
www.teva.se

Ulrika Zaki, Produktchef
Tel: 010-16 50 346
E-mail: ulrika.zaki@teva.se

Hälso- och sjukvårdspersonal samt patienter bör kontakta Teva Sweden AB vid frågor kring:

- rapportering av kvalitetsproblem och/eller alla typer av biverkningar hos patienter som använder Trisenox koncentrat för infusion
- informationen i detta brev eller kring säker och effektiv användning av Trisenox koncentrat för infusion

Rapportering av misstänkta biverkningar
Hälso- och sjukvårdpersonal ska i enlighet med gällande nationella föreskrifter rapportera misstänkta biverkningar till Läkemedelsverket (elektronisk blankett och instruktioner finns på www.lakemedelsverket.se).

Bilagor

- Produktinformation för Phenasen (på engelska)
- Trisenox och Phenasen; skillnader i produktinformation (på engelska)

Med vänliga hälsningar
Teva Sweden AB

Ulrika Zaki
Produktchef

Annika Gustavsson
Head of Commercial Quality Nordic

PRODUCT INFORMATION

PHENASEN®
Arsenic Trioxide Injection 10 mg in 10 mL

NAME OF THE MEDICINE

arsenic trioxide

The molecular weight of the compound is 197.84 and the CAS registry number is 1327-53-3. The molecular formula is As_2O_3.

DESCRIPTION

PHENASEN is a clear and colourless solution. Each 10 mL contains 10 mg arsenic trioxide as the active ingredient. It also contains sodium hydroxide and water for injections. Hydrochloric acid is added for pH adjustment. It is a sterile solution for single use and contains no antimicrobial preservative. The pH range of PHENASEN is 5.0-8.5. PHENASEN must be diluted before use.

PHARMACOLOGY

Pharmacodynamics

The precise molecular and cellular mechanisms underlying the pharmacodynamics of arsenic trioxide in acute promyelocytic leukaemia (APL) are uncertain. Arsenic trioxide can induce partial differentiation and apoptosis of leukaemic cells *in vitro.* There is also evidence that its other known pharmacological effects (degradation of specific APL fusion transcripts, anti-proliferation, inhibition of angiogenesis) may contribute to efficacy in APL.

Pharmacokinetics

Absorption/Distribution

Arsenic trioxide given by intravenous injection is rapidly distributed. In the blood, arsenic trioxide diffuses from plasma into red blood cells and 95-97% is bound to haemoglobin. Arsenic trioxide is distributed into sulphur-rich tissues such as bone marrow, hair, nails and skin where it accumulates with repeated dosing.

Following an initial dose of 10 mg intravenously over two hours, peak plasma levels of total arsenic range from 5.54 to 7.30 micromoles of arsenic/L at 0.9 hours. Continuous administration of arsenic trioxide over a period of thirty days does not alter the pharmacokinetic behaviour. Increased amounts of arsenic appeared in the urine.

Metabolism

The metabolism of arsenic trioxide involves reduction of pentavalent arsenic to trivalent arsenic by arsenate reductase and methylation of trivalent arsenic to monomethylarsonic acid and monomethylarsonic acid to dimethylarsinic acid by methyltransferases. The main site of methylation reactions appears to be the liver. Arsenic is stored mainly in liver, kidney, heart, lung, hair and nails.

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, and 4A9/11.

Excretion

The metabolites monomethylarsonic acid, dimethylarsinic acid and arsenite are mainly excreted in the urine. Arsenic is excreted in the urine with a daily excretion accounting for approximately 1% to 8% of the total daily dose administered but may range higher. Urinary excretion continues after withdrawal of the drug although the amount excreted is decreased. Studies with radiolabelled arsenic trioxide have demonstrated that after oral administration of 0.06 ng arsenic, approximately 60% of the radioactivity was recovered in the urine within 8 days.

The mean plasma elimination $t_{1/2}$ value in patients receiving arsenic trioxide was 92 hours. This 92-hour plasma elimination half-life is consistent with the reported 3 to 5 day urinary excretion half-life for arsenic.

Arsenic trioxide content in hair and nails increases gradually during therapy and the concentrations may reach 2.5 to 2.7 micrograms per gram of tissue at complete remission which is five to seven times that before treatment. The content of arsenic in hair and nails decreases following cessation of treatment.

CLINICAL TRIALS

In relapsed or refractory APL

Studies using arsenic trioxide in APL commenced in the early 1990s in China. In 1997 the first studies were undertaken in the US in the treatment of APL resistant to all-trans retinoic acid (ATRA, Australian approved name- Tretinoin) and anthracycline therapy. Six case series in 115 patients provide the best evidence for the efficacy of arsenic trioxide in APL that have relapsed or are refractory to ATRA, with or without an anthracycline.

Table 1. Results of selected studies in patients relapsed or refractory to ATRA/anthracycline therapy

Trial	N	Dose *mg/d*	CR %	Time to CR *days*	MR %	Progression Free Survival %	Overall Survival %
Soignet SL 1998	12	0.16/kg	92	47	67	ns	ns
Soignet SL 2001	40	0.15/kg	85	59	65	56@18m	66@18m
Shen ZX 1997	10	10	90	38	ns	ns	ns
Niu C 1999	31[1]	10	84	ns	21	ns	50@12m
Shen Y 2001	20	0.08/kg	80	ns	0	79@12m	93@12m
Lazo G 2003	12	0.15/kg	100	52	100	67@24m	83@24m

[1] Includes 10 patients from trial Shen ZX 1997
CR-Complete Remission-disappearance of all leukaemic myeloblasts and promyelocytes and < 5% overall myeloblasts by morphological examination of the marrow.
MR-Molecular Response- tested negative for the PML-RARα fusion transcript by real-time reverse transcription polymerase chain reaction (RT-PCR) assay.
Progression Free Survival- time in remission.
m - months
ns - not stated

In the majority of studies the complete remission rate is greater than 85%. The remission rate reduces over time and the results vary.

In previously untreated/*de novo* APL

APML4

In Australia, the Australasian Leukaemia and Lymphoma Group (ALLG) conducted the APML4 study, an open-label phase 2, multicentre trial in 124 patients including 4 children (only) with *de novo* APL were studied from 2004 to 2009. The median age of patients was 44 years. 19% of the enrolled patients were in high risk category; 54% were in the intermediate risk category 27% were in low risk category as defined by Sanz risk stratification. The APML4 study did not have a control arm but used the historical comparison of the APML3 study with ATRA and chemotherapy. PHENASEN was administered at 0.15 mg/kg/day (for detailed dosage regimen, refer to DOSAGE AND ADMINISTRATION).

The primary objectives of APML4 were to evaluate the effect of a chemotherapy protocol consisting of PHENASEN (arsenic trioxide) added to standard induction (ATRA plus intensive idarubicin) with two cycles of consolidation with ATRA plus PHENASEN on the time to relapse; and to assess the effect of obligatory use of prednisone (or prednisolone) and aggressive haemostatic support, during induction on the early death rate.

124 (62 female and 62 male) patients were evaluable for assessment of the CR rate. 112/124 (90.3%) completed induction and a further 4/124 did not complete induction but attained complete remission. All 112 patients who completed induction achieved molecular CR by the end of the 2nd consolidation cycle (CON2). 88% of these 112 patients completed all 8 maintenance cycles. The observed CR rate was 93.5% (95% CI: 87.9% – 97.2%). Of 112 patients evaluable for time to relapse analyses, 4 suffered molecular relapse and 1 suffered haematological relapse. The observed annual relapse-free rates measured from the end of CON2 were as follows: 1 and 2 years 97.3% (95% CI: 91.8% – 99.1%); 3, 4 and 5 years 95.4% (95% CI: 89.3% –98.1%). The observed overall survival rates were as follows: 1 year 96.0% (95% CI: 90.6% –98.3%); 2, 3, 4 and 5 years 94.3% (95% CI: 88.5% – 97.3%). -; The observed event-free survival rates were as follows: 1 year 88.7% (95% CI: 81.7% – 93.1%); 2 years 87.9% (95% CI: 80.7% – 92.5%); 3, 4 and 5 years 86.1% (95% CI: 78.6% – 91.1%).

One of the primary endpoints 'early death' rate in APML3 was 7.1% (5 of 70) and in APML4 it was 3.2% [(4 of 124 patients); this difference was not statistically significant (OR = 0.44; 95% CI: 0.08 to 2.10; P = 0.29). The cause of death in 2 of the 4 in APML4 and 7 of the 8 in APML3 was haemorrhage. Therefore there appears to be a smaller number of deaths linked to haemorrhage in APML4, in which obligatory corticosteroids and aggressive haemostatic support were provided during the induction phase.

Lo-Coco *et al*, 2013 (Lo-Coco)

The Lo-Coco, open-label, comparative, multi-centre, randomised phase 3 study aimed to show non-inferiority of ATRA + arsenic trioxide, for induction and consolidation relative to ATRA + chemotherapy. 162 patients with newly diagnosed, low-to-intermediate risk APL were studied from October 2007 to September 2010 with a median follow up of 34.4 months (range, 0.5 to 55.8). The comparator arm of this study included a low dose chemotherapy and ATRA regimen as maintenance therapy. The Intention-to-treat analysis (ITT) was in 156 (80 female and 76 male) patients. Median age of patients included in the study was 45 years.

Of the 150 evaluable patients, 97% in the ATRA + arsenic trioxide group (72 of 74) were alive and free of events at 24 months, as compared with 86% in the ATRA + chemotherapy group (65 of 76) (difference, 11% 95% CI: 2 to 22). The observed advantage in the 2-year event-free survival (which was the primary efficacy endpoint) with ATRA + arsenic trioxide compared to ATRA + chemotherapy (97% vs 86%) appears to be due mainly to lower mortality from causes other than relapse, probably as a consequence of reduced severe hematologic toxicity together with similar anti-leukaemic efficacy. The study reported haematological CR in all (100%) ATRA+ arsenic trioxide patients after a median 32 days of induction.

Both the Lo-Coco and APML4 studies used arsenic trioxide at a dose of 0.15 mg/kg/day however, in the Lo-Coco study idarubicin was omitted from the induction therapy and ATRA and arsenic trioxide were used in an extended consolidation therapy period of 28 weeks. The Lo-Coco dosage regimen also omitted the 2 year maintenance therapy consisting of ATRA + 6-mercaptopurine (6MP) ± methotrexate (MTX) utilised in the APML4 regimen.

INDICATIONS

For the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

For the induction of remission and consolidation in patients with previously untreated acute promyelocytic leukaemia (APL) in combination with *all-trans* retinoic acid (ATRA) and/or chemotherapy and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

CONTRAINDICATIONS

PHENASEN is contraindicated in patients who are hypersensitive to arsenic or any of the excipients (see DESCRIPTION).

PRECAUTIONS

PHENASEN should be administered under the supervision of a physician experienced in the management of patients with acute leukaemia.

APL Differentiation Syndrome

Some patients with APL treated with arsenic trioxide experience symptoms similar to a syndrome called retinoic acute promyelocytic leukaemia (RA-APL) syndrome 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. The first signs that could suggest the development of the APL differentiation syndrome are unexplained fever, dyspnoea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities. The management of the syndrome has not been fully studied, but high dose steroids have been used at the first suspicion of the APL differentiation syndrome and appear to mitigate signs and symptoms.

In APML4, an obligatory part of the treatment protocol was use of prednisone or prednisolone, 1 mg/kg/day, on days 1-10, and beyond day 10 if WCC was elevated >10 x 10^9 / L or if there were signs of APL differentiation syndrome. The APML4 study protocol included APL differentiation syndrome as the most serious and potentially fatal side effect of ATRA. Whenever the features of APL differentiation syndrome developed, ATRA and/or arsenic trioxide doses were temporarily ceased or reduced. When it was time to restart ATRA and/or arsenic trioxide therapy the dose of ATRA was reduced to 25 mg/m^2/day for 14 days and the dose of arsenic trioxide was reduced to 0.08 mg/kg/day. In particular, the compulsory use of prednisone (or

prednisolone) as prophylactic therapy and the delayed introduction of arsenic trioxide on day 9 of the induction therapy was expected to almost completely eliminate the severest form of APL differentiation syndrome.

In Lo-Coco trial, prednisone at a dose of 0.5 mg/kg/day was administered from day 1 until the end of induction therapy as a prophylaxis therapy for APL differentiation syndrome. Where features of APL differentiation syndrome occurred, the dose of arsenic trioxide was reduced to 0.08 mg/kg/day or ceased temporarily and ATRA was ceased depending on clinical severity. Dexamethasone, 10 mg every 12 hours iv was promptly started until the signs and symptoms of APL differentiation syndrome had disappeared for a minimum of 3 days. Furosemide was given when clinically required. As soon as the symptoms of APL differentiation syndrome disappeared and the patients' clinical conditions improved, the treatment with ATRA and/or arsenic trioxide was resumed at 50% of the previous dose for the first 7 days. Thereafter, in the absence of worsening of the previous toxicity, ATRA and/or arsenic trioxide was resumed at full dosage. Whenever the APL differentiation syndrome symptoms reappeared, ATRA and arsenic trioxide doses were reduced as described above.

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. The risk of *torsade de pointes* is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of *torsade de pointes*, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-depleting diuretics, or other conditions that result in hypokalaemia or hypomagnesaemia. One patient (also receiving amphotericin B) had *torsade de pointes* during induction therapy for relapsed APL with arsenic trioxide.

QT/QT$_c$ Prolongation: QT prolongation should be expected during treatment with arsenic trioxide and *torsades de pointes* as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a 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 arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age.

Complete AV block: Complete AV block has been reported with arsenic trioxide in the published literature including a case of a patient with APL.

ECG and Electrolytes: Monitoring Recommendations
Patients with congestive heart failure should not be administered arsenic trioxide, except when the benefit outweighs the risk. Prior to initiating therapy with PHENASEN, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using arsenic trioxide. During therapy with arsenic trioxide, potassium concentrations should be kept above 4 mmol/L and magnesium concentrations should be kept above 0.8 mmol/L. Patients who reach an absolute QT interval > 500 msec should be reassessed and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending arsenic trioxide therapy should be considered. If syncope, rapid or irregular heart beat develops, the patient should be hospitalised for monitoring and serum electrolytes should be assessed. Arsenic trioxide therapy should be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of arsenic trioxide on the QTc interval during the infusion.

Peripheral neuropathy
Peripheral neuropathy has been associated with the use of arsenic trioxide. In the largest case series (Soignet SL, 2001 - see CLINICAL TRIALS) one patient (out of 40) experienced grade 3 neuropathy and required discontinuation of arsenic trioxide treatment. Patients should be monitored periodically for symptoms or signs of neuropathy. Patients on continuing arsenic trioxide treatment may be at greater risk.

Hepatotoxicity
During the APML4 study, the dose of arsenic trioxide was decreased to 0.08 mg/kg/day for grade 3 hepatotoxicity and temporarily discontinued for grade 4 hepatotoxicity. After temporary discontinuation arsenic trioxide was restarted at 0.08 mg/kg/day when the liver function test (LFT) improved to grade 2 or better. If no further deterioration occurred in the LFT after one week, the arsenic trioxide dose was increased back to 0.15 mg/kg/day.

The Lo-Coco *et al*, 2013 clinical trial defined hepatotoxicity as an increase in serum bilirubin and/or serum glutamic oxaloacetic transaminase (SGOT) and/or alkaline phosphatase >5 times the normal upper level. Hepatotoxicity was managed with temporary discontinuation and subsequent dose adjustment of ATRA and/or arsenic trioxide. As soon as serum bilirubin and/or SGOT and/or alkaline phosphatase decreased to below 4 times the normal upper level, treatment with ATRA and/or arsenic

trioxide was resumed at 50% of the preceding daily dose during the first 7 days. Thereafter, in the absence of worsening of the previous toxicity, ATRA and/or arsenic trioxide was resumed at the normally prescribed dosage. In case of reappearance of hepatotoxicity, ATRA and/or arsenic trioxide were permanently discontinued.

Patients with renal or hepatic impairment

Safety and effectiveness of arsenic trioxide in patients with renal and hepatic impairment have not been studied. Particular caution is needed in patients with renal failure receiving arsenic trioxide, as renal excretion is the main route of elimination of arsenic.

Hyperleukocytosis

Arsenic trioxide has been investigated in 40 relapsed or refractory APL patients, previously treated with an anthracycline and a retinoid regimen, in an open-label, single-arm, non-comparative study (Soignet SL, 2001). Patients received arsenic trioxide 0.15 mg/kg/day intravenously over 1 to 2 hours daily until the bone marrow was cleared of leukaemic cells or up to a maximum of 60 days. In this study in relapsed or refractory APL patients, treatment with arsenic trioxide was associated with the development of hyperleukocytosis (≥ 10 x 10^9 /L) in some 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 10^9 /L, except in one patient who had a WBC count of 22 x 10^9 /L during consolidation. Twenty patients (50%) experienced leukocytosis; however, in all these patients, the WBC count was declining or had normalised by the time of bone marrow remission and cytotoxic chemotherapy or leukopheresis was not required.

In APML4 three *de novo* APL patients demonstrated marked hyperleukocytosis when treated with arsenic trioxide combination therapy. Hyperleukocytosis regressed following anthracycline administration, no major complications were observed. As a safeguard against hyperleukocytosis, prednisone (or prednisolone) 1mg/kg/day was instituted on day 1 for at least 10 days in all patients. Prednisone was continued until the WCC fell below 10X 10^9/L.

In *de novo* APL the Lo-Coco trial reported leukocytosis during induction therapy in 35 of 74 patients in the ATRA with arsenic trioxide group (47%) and in 19 of 79 patients in the ATRA with chemotherapy group (24%) (P = 0.007). All cases were successfully managed with hydroxyurea after treatment initiation at the dosage of 500 mg/qid for WBC between 10 and 50 x10^9/L, and 1.0 g/qid for WBC >50 x10^9/L. Hydroxyurea was discontinued when WBC count decreased to <10 x10^9/L.

Effects on Fertility

The effects of arsenite on fertility have not been systematically studied. Men and women of childbearing potential must use effective contraception during treatment with PHENASEN.

Use in Pregnancy

Category X: Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

PHENASEN should not be given to patients who are pregnant. Pregnancy test prior to the treatment with PHENASEN should be considered.

In hamsters, rats and mice, parenteral administration of arsenite during the period of organogenesis produces malformations, including neural tube, eye, facial, genitourinary and skeletal defects, at respective single doses of *ca* 2-13 fold the clinical dose on a body surface area basis; no-effect dose levels were not established. Arsenite treatment of mice during gestation has also produced a widespread tumorigenic response in offspring. The effects of arsenic trioxide injection on human pregnancy are not known, but the results of the animal studies indicate that this treatment should not be given to pregnant women.

Use in Lactation

It is not known whether arsenite and/or its metabolites are excreted in milk. Arsenic trioxide should not be administered to lactating women.

Paediatric Use

There are limited clinical data on the paediatric use of arsenic trioxide. Of 5 patients below the age of 18 years (age range: 5 to 16 years) who received a dose of 0.15 mg/kg/day for relapsed/refractory APL, 3 achieved a complete response. In two published studies in children with *de novo* APL (age range 5 – 15 years; 11 and 19 children respectively) treated with single agent arsenic trioxide, 89.5 % and 91.0% of the children achieved CR, with overall response reaching 91% at 30 months and 84% at 5 years respectively.

Safety and effectiveness in paediatric patients below the age of 5 years has not been studied.

Use in the Elderly
There is limited clinical data on the use of arsenic trioxide in the elderly population. Elderly patients have a greater risk of reduced renal function. Because renal excretion is the main route of elimination of arsenic, particular caution is needed in these patients.

Genotoxicity
Positive findings have been observed with arsenite in genotoxicity assays, including gene mutation in mammalian cells, clastogenicity *in vitro* and *in vivo,* and cell transformation. Positive genotoxicity findings have also been reported for the human metabolite dimethylarsinic acid (DMA).

Carcinogenicity
Epidemiological studies have found considerable evidence for an association between arsenic exposure and increased incidence of tumours, especially of the skin, lung and some internal organs. The mechanism of action is not fully understood, but it is likely to involve carcinogenic methylated metabolites such as dimethylarsinic acid (DMA). Arsenite treatment of mice during gestation has produced a widespread tumorigenic response in offspring.

Effect on laboratory tests
The patient's electrolyte, haematologic and coagulation profiles should 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.

ECGs should be obtained weekly, and more frequently for clinically unstable patients, during induction and consolidation.

INTERACTIONS WITH OTHER MEDICINES

No assessments of drug interactions have been made. Caution is advised when PHENASEN is used with medications that:

- can prolong the QT interval (e.g. certain antiarrhythmics, thioridazine)
- lead to electrolyte abnormalities (e.g. diuretics, amphotericin B)

Arsenic trioxide should not be used concomitantly with ziprasidone or pimozide because of potential additive effects on prolongation of the QT intervals.

ADVERSE EFFECTS

Death
Sudden death, sometimes early in the treatment with arsenic trioxide has occurred. Autopsies have sometimes failed to identify a cause of sudden death. Cerebral haemorrhage has been the cause of death in three patients. Another patient on whom an autopsy was not performed became asystolic and died while on continuous cardiac telemetry. The level of arsenic trioxide excreted in the urine does not seem to be related as a cause of death. Adverse reactions are ranked below using the following convention: very common (≥ 1/10); common (≥ 1/100 < 1/10); uncommon (≥ 1/1,000 < 1/100).

Table 2. Adverse Reactions

Organ System	Adverse Reaction
General	
Very Common	Fever[1]
Common	Fatigue, APL differentiation syndrome
Uncommon	Chest pain, pain
Gastrointestinal	
Common	Nausea, vomiting, diarrhoea, abdominal pain, mucositis
Respiratory	
Common	Cough, sore throat, dyspnoea, pleuritic pain
Uncommon	Pulmonary alveolar haemorrhage, pleural effusion, hypoxia
Neurological	
Common	Headache, insomnia, peripheral neuropathy, paraesthesia, mood alteration, musculoskeletal pain, seizures
Metabolic	
Very common	Hepatotoxicity
Common	Hypokalaemia, hyperglycaemia, increase in AST, ALT, GGT or bilirubin, liver dysfunction
Uncommon	Hypermagnesaemia, hypernatraemia, ketoacidosis

Table 2. Adverse Reactions (continued..)

Organ System	Adverse Reaction
Cardiovascular	
Very Common	Arrhythmia including non-sustained ventricular tachycardia, premature ventricular contractions, QT_c-prolongation
Common	*torsade de pointes*, ventricular tachycardia[2]
Uncommon	CVA (cerebral vascular accident), pericardial effusion
Haematological	
Very common	Leukocytosis, Neutropenia, thrombocytopenia
Common	Febrile neutropenia, haemorrhage, thrombosis
Uncommon	leucopenia vasculitis
Genitourinary	
Uncommon	Renal failure
Skin	
Common	Rash, Pruritus
Uncommon	Dermatitis, erythema
Immunological	
Rare	Immune suppression causing herpes zoster
Infection	
Very Common	Infection
Musculoskeletal, connective tissue and bone disorders	
Common	Bone pain, arthralgia, musculoskeletal pain
Investigations	
Common	ECG QT prolongation, increase in ALT, increase in aspartate amino transferase
Uncommon	Hyperbilirubinaemia, hypomagnesaemia

[1.] Fever and dyspnoea with one or more of weight gain, generalised oedema, respiratory failure or lung infiltrates. Resolved with dexamethasone. [2.] A case of *torsade de pointes* resolved spontaneously.

Seven relapsed and/or refractory APL patients treated with arsenic trioxide developed polyneuropathy compatible with chronic arsenic toxicity while in maintenance therapy and one had marked distal muscular atrophy (Huang *et al,* 1998). Reactions are often mild and there may be no need to interrupt arsenic trioxide therapy. Adverse effects usually resolve after therapy is completed.

While all the newly diagnosed/de novo APL patients experienced AEs in the APML4 trial, the majority of these AEs were related to the prescribed protocol treatment and were expected. Ninety one of the 124 patients commencing induction treatment (73%) experienced SAEs and 69% experienced more than 1 SAE.

Within the clinical setting of APL, and based on the protocol prescribed chemotherapy regimen, changes to laboratory parameters were both expected and manageable. No unexpected or new laboratory abnormalities were noted, and patients were clinically managed according to the usual practice of each clinical trial site. Overall, patients tolerated the APML4 protocol prescribed regimen. The use of an aggressive haemostatic/blood product support protocol during the induction cycle contributed to a reduction in fatal haemorrhage, and the use of obligatory corticosteroids may have contributed to the absence of APL differentiation syndrome -associated early deaths.

In the Lo-Coco trial, ATRA + arsenic trioxide combination resulted in more frequent prolongation of the QTc interval and liver-function abnormalities. Hepatotoxic effects appeared to be manageable with temporary discontinuation of the study medication and subsequent dose adjustments; the use of hydroxyurea was sufficient to counteract hyperleukocytosis.

DOSAGE AND ADMINISTRATION

Method of administration

0.15 mg/kg/day diluted with 100 - 250 mL of 5% glucose injection or 0.9% sodium chloride injection and administered intravenously (iv) over two hours.

Cycles of treatment are given to achieve complete remission, defined as the complete disappearance of all leukaemic myeloblasts and promyelocytes and < 5% overall myeloblasts by morphological examination of the marrow. After induction

of remission, consolidation cycles may be given, and maintenance therapy considered. PHENASEN may be given in combination with all-trans retinoic acid (ATRA) and/or chemotherapy.

In patients with newly diagnosed/ *de novo* APL combination treatment

PHENASEN may be given in combination with all-trans-retinoic acid (ATRA) and/or chemotherapy. Dosage regimens for high risk patients and low to intermediate risk patients are described in Table 3 and Table 4 respectively.

Table 3. Dosage regimen for High risk patients

Category of patients	Treated with	Induction (Cycle 1)	Consolidation (Cycle 2): Commences 3-4 weeks after completion of cycle 1	Consolidation (Cycle 3): Commences 3-4 weeks after completion of cycle 2
Patients with WBC count > 10 x 10^9/L	PHENASEN	0.15 mg/kg/day from day 9 to 28 days. Last dose on day 36	0.15 mg/kg/day from day 1 to 28 days	0.15 mg/kg/day for 5 days/week (5 days on, 2 days off for a total of 5 cycles) i.e.: days 1-5, 8-12, 15-19, 22-26, and 29-33
	ATRA (Tretinoin)	Dose as per the prescribing information of ATRA.		

Chemotherapy with idarubicin (iv) on Days 2, 4, 6 and 8. The idarubicin dose is age-dependent and given at the induction phase only based on a patients' ability to tolerate.

It is strongly recommended that during induction patients are treated with prednisone (or prednisolone); 1 mg/kg/day for at least 10 days. Aggressive platelet and plasma support should also be considered to maintain haemostatic targets.

For patients in CR after the 3 cycles of induction/consolidation, maintenance consisting of ATRA from Day 1–14, followed by 6-mercaptopurine (6MP) and methotrexate (MTX) both from Day 15-90 (each cycle 3 months) may then be administered for 24 months.

Table 4. Dosage regimen for Low-to-intermediate risk patients

Category of patients	Treated with	Induction (Cycle 1)	Consolidation (4 cycles)
WBC count ≤ 10 x 10^9/L	PHENASEN	0.15 mg/kg/day from day 1 until haematological CR or for a maximum of 60 days. If no haematological CR is achieved by day 60 discontinue treatment.	0.15 mg/kg/day 5 days per week. 4 weeks on and 4 weeks off, for a total of 4 cycles
	ATRA (Tretinoin)	Dose as per the prescribing information of ATRA.	

In the Lo-Coco trial, marrow samples were collected at the end of the third consolidation cycle and tested by RT-PCR for assessment of molecular remission. Patients who did not achieve molecular remission at the end of the entire consolidation programme were considered as molecular resistant and taken off the treatment.

Dose Modification in newly diagnosed/de novo APL patients: Please refer to the PRECAUTION section.

In patients refractory to, or relapsed from retinoid and anthracycline therapy:

Induction Treatment Therapy

For induction, a daily infusion of 0.15 mg/kg/day is continued until bone marrow remission is obtained. If bone marrow remission is not obtained by day 60, dosing must be discontinued.

Consolidation Treatment Therapy

An additional course beginning consolidation of treatment may begin 3-4 weeks after completion of the induction cycle. The dose is the same as for induction, except that 25 daily doses over a period of up to 5 weeks are given.

There are no data on the use of arsenic trioxide in patients with renal and hepatic impairment. Caution is recommended in renal impairment since renal excretion is the main route of elimination of arsenic trioxide. Caution is also required in hepatic impairment since the liver is the major site of detoxification of arsenic trioxide.

Dose Modification in refractory to, or relapsed from retinoid and anthracycline therapy
Treatment with PHENASEN must be interrupted, adjusted, or discontinued before the scheduled end of therapy at any time that a toxicity grade 3 or greater, based on the National Cancer Institute Common Toxicity Criteria, is observed and judged to be possibly related to arsenic trioxide treatment. Patients who experience such reactions that are considered PHENASEN 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 3 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.

Drug Stability

Once diluted the solution should be used as soon as possible. It is a sterile solution for single use and contains no antimicrobial preservative. If storage is necessary the prepared solution should be refrigerated between 2°C and 8°C and stored for no longer than 24 hours before discarding.

Drug Compatibilities

PHENASEN is compatible with 5% glucose injection and 0.9% sodium chloride injection.

OVERDOSAGE

Treatment of overdose

If symptoms of serious acute arsenic toxicity appear, the drug should be immediately discontinued and chelation therapy should be considered. Other anti-arsenical treatment may be considered.

PRESENTATION AND STORAGE CONDITIONS

PHENASEN (Arsenic Trioxide Injection 10 mg/10 mL) is presented in 10 mL vials in cartons of 10.

AUST R 152760

Phebra product code- INJ008

Store below 30ºC. Proper safe handling and disposal should be observed by medical staff.

NAME AND ADDRESS OF THE SPONSOR

Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

Distributed in New Zealand by AFT Pharmaceuticals Ltd. PO Box 33-203 Auckland.

Arsenic Trioxide is sold in Australia and New Zealand under license from Cephalon, Inc.

POISON SCHEDULE OF THE MEDICINE

Schedule 4- Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 13th May 2009
DATE OF MOST RECENT AMENDMENT: 6th October 2016

Annexe

Amsterdam, July 26th, 2017

IMPORTANT DRUG INFORMATION

Subject: Trisenox and Phenasen (arsenic trioxide)
1 mg/ml concentrate for solution for infusion:
Product Information differences

PRODUCT INFORMATION: Phenasen

Each 10 ml contains 10 mg arsenic trioxide as the active ingredient. It also contains sodium hydroxide and water for injections. Hydrochloric acid is added for pH adjustment. It is a sterile solution for single use and contains no antimicrobial preservative. The pH range of Phenasen is 5.0-8.5. Phenasen must be diluted before use. Phenasen (Arsenic Trioxide Injection 10 mg/10 ml) is presented in 10 ml vials in cartons of 10. Store below 30ºC.

THERAPEUTIC INDICATIONS

- For the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

- For the induction of remission and consolidation in patients with previously untreated acute promyelocytic leukaemia (APL) in combination with *all-trans* retinoic acid (ATRA) and/or chemotherapy and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression (the indication is not limited to low-intermediate risk APL patients).

DOSAGE AND ADMINISTRATION
Method of administration
0.15 mg/kg/day diluted with 100 - 250 ml of 5% glucose injection or 0.9% sodium chloride injection and administered intravenously (iv) over two hours.

Once diluted the solution should be used as soon as possible. It is a sterile solution for single use and contains no antimicrobial preservative. If storage is necessary the prepared solution should be refrigerated between 2°C and 8°C and stored for no longer than 24 hours before discarding.

Dosage
Newly diagnosed APL patients are divided in:

High risk APL patients: ATO in combination with ATRA + chemotherapy (this indication is not included in Trisenox SmPC).

Low-to intermediate risk APL patients: ATO combination with ATRA.

- Induction: 0.15 mg/kg/day from day 1 until haematological CR or for a maximum of 60 days. If no hematological CR is achieved by day 60 discontinue treatment. (the schedule and dose is the same as in Trisenox SmPC).

- Consolidation: 0.15 mg/kg/day 5 days per week. 4 weeks on and 4 weeks off, for a total of 4 cycles (the schedule and dose is the same as in the Trisenox SmPC).

Relapsed/refractory acute promyelocytic leukaemia (APL)

- Induction Treatment: for induction, a daily infusion of 0.15 mg/kg/day is continued until bone marrow remission is obtained. If bone marrow remission is not obtained by day 60, dosing must be discontinued (this schedule is slightly different compared with Trisenox SmPC, the dose is the same).

- Consolidation Treatment: an additional course beginning consolidation of treatment may begin 3-4 weeks after completion of the induction cycle. The dose is the same as for induction, except that 25 daily doses over a period of up to 5 weeks are given (the schedule and dose is the same as in the Trisenox SmPC).

PRODUCT INFORMATION: Trisenox

Trisenox 1 mg/ml concentrate for solution for infusion. One ml of Trisenox contains 1 mg of arsenic trioxide. Nature and contents of container: Type I borosilicate glass ampoule containing 10 ml of concentrate. Each pack contains 10 ampoules. List of excipients: Sodium hydroxide, Hydrochloric acid (as pH adjuster), Water for injections. Special precautions for storage: Do not freeze.

THERAPEUTIC INDICATIONS

It is indicated for induction of remission, and consolidation in adult patients with:

• Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA).

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

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

DOSAGE AND ADMINISTRATION

Method of administration

Trisenox 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 ampoule. It is for single use only, and any unused portions of each ampoule must be discarded properly. Do not save any unused portions for later administration.

After dilution in intravenous solutions, Trisenox is chemically and physically stable for 24 hours at 15°C-30°C and 48 hours at refrigerated (2°C-8°C) temperatures. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Dosage

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

- Induction treatment schedule: 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 discontinue
- Consolidation schedule: 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.

Relapsed/refractory acute promyelocytic leukaemia (APL)

- Induction treatment schedule: 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.
- Consolidation schedule: 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.

COMMENT:
Phenasen and Trisenox: both products contain arsenic trioxide as the active ingredient in the same concentration: 10 ml contains 10 mg arsenic trioxide, however:

- Phenasen presentation is a vial
- Trisenox presentation is an ampoule

INDICATION:
newly diagnosed APL patient:

- Phenasen: the indication is not limited to low-intermediate risk APL patients
- Trisenox: the indication is limited only in low-intermediate risk APL patients

Moreover, in newly diagnosed APL patient, Phenasen may be given in combination with all-trans-retinoic acid (ATRA) and/or chemotherapy, depends on the risk stratification. Instead in Trisenox SmPC only in combination with ATRA in low-to-intermediate risk APL patients.

SCHEDULE AND DOSAGE:

- Phenasen: there is a different schedule for the newly diagnosed APL patients based on the risk stratification:
    - High risk (white blood cell count, ≥ 10 x 10^9/L) include the combination of ATRA + chemotherapy + ATO. This indication is not included in the Trisenox SmPC.
    - Low-to intermediate risk (white blood cell count, ≤ 10 x 10^9/L) include ATRA + ATO. The schedule and dose of low-to intermediate risk APL patients is the same in the Phenasen and Trisenox product information.
- Phenasen: there is a different schedule on the relapse/refractory APL patients:
    - Induction is 60 days in Phenasen product information, it is 50 days in Trisenox SmPC
    - Consolidation: the schedule and dose is the same in the Phenasen and Trisenox product information.
- Dose Modification due to treatment related adverse event (grade 3 or greater, based on the National Cancer Institute Common Toxicity Criteria): Patients 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. However there is a small difference on time of (re)-escalation of 100% of the dosage:
    - Phenasen: If the toxic event does not recur within 3 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.

- Trisenox: 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.

- Moreover for symptoms related to QT prolongation, in the Trisenox SmPC. 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 Trisenox 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. This specific (re)-dose escalation in two steps in patients with syncope and irregular heartbeat cease and QT prolongation is not mentioned in the Phenasen product Information.

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