1 PRODUCT NAME

PHENASEN® 10 mg/10 mL concentrated solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL of PHENASEN concentrated injection contains 10 mg arsenic trioxide.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Concentrated solution for infusion

4 CLINICAL PARTICULARS

4.1 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.

4.2 Dose and method of 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 1 and Table 2 respectively.

Table 1. 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 for 28 days. Last dose on day 36	0.15 mg/kg/day from day 1 for 28 days	0.15 mg/kg/day for 5 days/week (5 days on, 2 days off for a total of 5 weeks) 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 patient's 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 2. 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 Special warnings and precautions for use 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.

4.3 Contraindications

PHENASEN is contraindicated in patients who are hypersensitive to arsenic or any of the excipients (see Section 6.1 List of Excipients).

4.4 Special warnings and precautions for use

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 Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety) 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 ($\geq 10 \times 10^9$ /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 $< 10 \times 10^9$ /L, except in one patient who had a WBC count of 22×10^9 /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 10×10^9/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 50×10^9/L, and 1.0 g/qid for WBC >50×10^9/L. Hydroxyurea was discontinued when WBC count decreased to <10×10^9/L.

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.

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.

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines

Unknown

4.8 Undesirable 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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100) and rare (≥1/10,000 to < 1/1,000).

Table 3. 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 3. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX27

Mechanism of action

The precise molecular and cellular mechanisms underlying the pharmacodynamics of arsenic trioxide in acute promyelocytic leukaemia (APL) are uncertain.

Pharmacodynamic effects

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.

Clinical efficacy and safety

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 4. 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 section 4.2 Dose and method of 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.

5.2 Pharmacokinetic properties

Absorption

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.

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.

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.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, hydrochloric acid and water for injections.

6.2 Incompatibilities

None

6.3 Shelf life

Prior to first use: 36 months

In use: 24 hours

6.4 Special precautions for storage

Prior to first use: Store below 30°C.

In use: store between 2°C and 8°C.

6.5 Nature and contents of container

10 mL solution in a 10 mL clear type I glass vial with a rubber stopper and flip off seal in packs of 10 vials.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

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. Proper safe handling and disposal should be observed by medical staff.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

31 January 2019

10 DATE OF REVISION OF THE TEXT

23 July 2019

SUMMARY TABLE OF CHANGES

Date of Revision	Section changed	Summary of new information
31 January 2019	n/a	New
1 February 2019	8	Changed of sponsor
9 July 2019	1	Editorial update on the name of dosage form
	3	Editorial update on the name of dosage form
	4.2	Correction of the dosage regimen in table 1
	4.8	Minor editorial update
	5.1	Minor editorial update
	5.2	Minor editorial update
	6.6	Improve clarity for special precautions for disposal