Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Arsenic trioxide

Proprietary Product Name: Phenasen

Sponsor: Phebra Pty Ltd

December 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
APLDS	APL differentiation syndrome
APML3,APML4	ALLG APML trial codes, 3rd and 4th trials
AST	Aspartate amino transferase
ATO	Arsenic trioxide, As_2O_3
ATRA	All-trans retinoic acid
BaCT	Centre for Biostatistics and Clinical Trials
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CSR	Clinical study report
CT	chemotherapy
CTCAE	Common terminology criteria for adverse events
D	Daunorubicin
DFS	Disease free survival
DMSC	Data Management and Safety Committee
EC	Ethics committee
ECG	Electrocardiogram
EFS	Event-free survival
FAB	French-American-British, classification system
FFS	Failure Free Survival
FLT3	FMS-like tyrosine kinase-3
GCP	Good clinical practices
GGT	Gamma glutamine transferase
GI	Gastrointestinal
H	Homoharringtinone

Abbreviation	Meaning
HCR	Haematological complete remission
IDA	Idarubicin
ITT	Intention-to-treat
IV	Intravenous
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ND	Not done
OS	Overall survival
PML-RARα	Promyelocytic leukaemia – retinoic acid receptor alpha fusion gene
PP	Per protocol
QTc	Corrected QT interval
RCT	Randomised controlled trial
RFS	Relapse free survival
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
TE	Thromboembolism
TGA	Therapeutic Goods Administration
TTR	Time to relapse
VZV	Varicella Zoster Virus
WBC	White blood cell count

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	24 August 2015
Date of entry onto ARTG	26 August 2015
Active ingredient(s):	Arsenic trioxide
Product name(s):	Phenasen®
Sponsor's name and address:	Phebra Ply Ltd 19 Orion Road, Lane Cove West, NSW 2066
Dose form(s):	Concentrated injection
Strength(s):	10 mg / 10 mL
Container(s):	Glass Type I Clear
Pack size(s):	10 x 10 mL vials
Approved therapeutic use:	*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.*
Route(s) of administration:	Intravenous infusion (IVI).
Dosage:	Cycles of treatment are given to achieve complete remission, defined as the complete disappearance of all Ieukaemic 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.
ARTG number (s):	152760

Product background

This AusPAR describes the application by the sponsor to extend the indications for Phenasen (arsenic trioxide (ATO)) to include use alongside idarubicin and/or ATRA (all-*trans* retinoic acid), in newly diagnosed acute promyelocytic leukaemia *(*APL) as follows[1]

> *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.*

Phenasen is currently approved for the following 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.*

Arsenic has been used in traditional Chinese medicine for two thousand years but the precise molecular and cellular mechanisms underlying the pharmacodynamics of ATO in acute promyelocytic leukaemia (APL) are uncertain. ATO can induce partial differentiation and apoptosis of Ieukaemic cells in vitro. There is also evidence that its other known pharmacological effects (degradation of specific APL fusion transcripts, antiproliferation, inhibition of angiogenesis) may contribute to efficacy in APL.

APL makes up 10 to 15% of acute myeloid leukemias and is distinguishable by, amongst other things, the reciprocally balanced chromosomal translocation t(15;17)(q22;q21) which creates *PML-RARA* and *RARA-PML* fusion genes and, consequently, the PML-RARA fusion protein.

In March 2014, the journal Best Practice & Research Clinical Haematology published a series of articles describing acute promyelocytic leukaemia.[2] A preface by Martin Tallman describes APL:

> *Acute promyelocytic leukemia (APL), once highly fatal, is now the most curable subtype of acute leukemia in adults. Even patients with high-risk disease defined as those presenting with a white blood cell count above 10,000/ml, have a very low relapse rate of approximately 10% in recent studies. All trans-retinoic acid (ATRA) and arsenic trioxide (ATO) are highly effective and the combination has proved curative without the requirement of additional cytotoxic chemotherapy in many patients. Nevertheless, there are a number of issues at the forefront of contemporary therapeutic strategies…*

One of these articles, by Iland et al[3], describes the evolution of ATRA and anthracycline therapy for APL and further describes the introduction of ATO into management of APL.

Because APL is easily distinguishable from other AML subsets, its epidemiology can be studied. There is a constant incidence with age after 20 years (APL also occurs in children and adolescents, constituting 5 to 10% of childhood AML in the USA); equal occurrence in males and females; and higher frequency in patients originating in Latin America.

No environmental or occupational risk factors are known but therapy related APL may account for 5 to 22% of cases. Therapy related APL typically develops less than 3 years

[1]The sponsor initially applied for the following new indication:

> *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 chemotherapy unless ATRA and/or chemotherapy is contraindicated.*

[2]Volume 27, issue 1, pages 1-80. <http://www.sciencedirect.com/science/journal/15216926/27/1>

[3] Iland HJ et al. Have all-trans retinoic acid and arsenic trioxide replaced all-trans retinoic acid and anthracyclines in APL as standard of care. Best Practice & Research Clinical Haematology 27 (2014) 39–52.

after a primary neoplasm (for example, breast or prostate cancer), when treated with anthracyclines, mitoxantrone or etoposide[4], that is, drugs that poison topoisomerase II.

Key drug targets in APL are described by Lehmann-Che et al (2014)[5] as follows:

> *Acute promyelocytic leukemia (APL) is driven by an oncogenic chromosomal translocation fusing the promyelocytic leukemia (PML) and retinoic acid receptor alpha (RARA) genes. APL responds to two targeted therapies: all-trans retinoic acid (ATRA) and arsenic trioxide. Arsenic binds to the PML moiety of the PML-RARA fusion, whereas ATRA binds to its RARA portion; each drug initiates biochemically independent degradation pathways. Degradation of RARA (or PML-RARA) follows transcriptional activation by ATRA. Arsenic trioxide initiates degradation of PML (or PML-RARA) by promoting PML aggregation into subnuclear domains implicated in senescence and apoptosis.*
>
> *Several studies in humans and mice have shown that ATRA and arsenic trioxide dramatically synergize for eradication of APL, presumably because this therapeutic association degrades PML-RARA more efficiently than either treatment alone.*

There is further comment in the current PI that safety and effectiveness in patients <5 years of age have not been studied.

ATRA is registered as tretinoin, and supplied as 10 mg capsules (Vesanoid, ARTG 53160). Vesanoid has the following indication:

> *Vesanoid should be used for induction of remission in acute promyelocytic leukaemia (APL; FAB classification AML-M3). Previously untreated patients as well as patients who relapse after or are refractory to standard chemotherapy (daunorubicin and cytosine arabinoside (ARA-C) or equivalent therapies) may be treated with Vesanoid. Following complete remission, consolidation full-dose chemotherapy should be employed. A loss of responsiveness to Vesanoid has been reported among patients maintained on Vesanoid. The median time to relapse for patients maintained on Vesanoid is 4 to 6 months.*

Idarubicin Ebewe (one of several registered idarubicin products) has the following indications on the Australian Register of Therapeutic Goods (ARTG):

> *Idarubicin Ebewe is indicated for use in acute myelogenous leukaemia (AML) in adults for remission induction in untreated patients or for remission induction in relapsed or refractory patients.*
>
> *Idarubicin Ebewe may be used in combination chemotherapy regimens involving other cytotoxic agents.*

Changes to the Phenasen PI, including the Dosage and Administration section were also proposed.

Regulatory status

Arsenic trioxide (ATO) has orphan status in Australia.[6]

An early application in 2004 to register Phenasen, based on published papers, did not succeed because of inadequate evidence of (a) safety and (b) manufacturing and quality control of the active pharmaceutical ingredient (API).

[4] Mistry A et al. DNA Topoisomerase II in therapy-related acute promyelocytic leukemia. NEJM 2005; 352: 1529-1538
[5] Lehmann-Che J et al. (2014). Resistance to Therapy in Acute Promyelocytic Leukemia. N Engl J Med 371:1170-1172
[6] <https://www.tga.gov.au/orphan-drugs#summary-a>

Re-submission for approval as monotherapy in relapsed/refractory disease was successful and Phenasen was registered on 7 May 2009 (ARTG ID 152760) for intravenous administration with the indication:

> *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.*

The sponsor has not applied to register Phenasen in any other country other than Australia. Arsenic trioxide has been available in the USA since 2000, in Europe since 2002, in the Australian market under special access scheme (schedule 5A of the Therapeutic Goods Regulations) since 1998.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

There was no requirement for a quality evaluation in a submission of this type.

The molecular formula is AS_2O_3 and the molecular weight of the compound is 197.84. The CAS registry number is 1327-53-3.

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 Injection. Hydrochloric acid is added for pH adjustment. It is a sterile solution for single use and contains no antimicrobial preservative. The pH of Phenasen is between 6 and 8. Phenasen must be diluted before use.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This submission was partly literature based and details of the published references submitted by the sponsor in support this application can be found in *Attachment 2 Extract from the CER*, under *References*.

Clinical rationale

APL is a rare disease, accounting for 5 to 15% of all the acute myelogenous leukemia in adults. APL has an incidence of 1,000 to 1,500 newly diagnosed patients a year in the USA and 700 to 800 in the European Union (EU). There are less than 100 cases of APL diagnosed in Australia each year. APL has equal incidence in men and women.

The majority of APL patients enter complete remission (CR) when treated with ATRA, which induces terminal differentiation of the leukaemic clone and simultaneously corrects the coagulopathy. However, ATRA therapy is associated with a potentially fatal capillary leak syndrome (retinoic acid syndrome or APL differentiation syndrome (APLDS). Furthermore, ATRA-induced remissions are not durable and continuous ATRA maintenance therapy is followed by the emergence of ATRA resistance. Randomised studies have confirmed the benefits of simultaneous ATRA and CT; the combined approach affords reciprocal protection against both coagulopathy aggravated by CT and the retinoic acid syndrome. The overall survival of APL patients prior to the introduction of ATRA was approximately 35% at 3 years, whereas it now exceeds 80% with combination therapy.

APL is uniquely associated with a t(15;17) reciprocal translocation, and disruption of the PML and RARα genes. Clinically the disease shows a propensity for life-threatening haemorrhage that is aggravated by cytotoxic chemotherapy (CT) and sensitivity to both ATRA and to ATO. Both ATRA and ATO exert their therapeutic activity through their action on so called Leukemia Initiating Cells and in particular to therapy induced degradation of the PML-RARα oncoprotein. As ATRA and ATO target distinct moieties of the PML/RARα fusion and as the degradation pathways are non-cross resistant, there is a synergistic activity of ATRA and ATO in this setting which provides a rationale for their use in combination.

The clinical evaluator commented that '*No clear clinical rationale has been provided to justify proposed use of ATO as single agent in newly diagnosed, previously untreated APL.*'

Guidance

On 28 February 2012, a pre-submission, scientific advisory meeting between the TGA and Phebra representatives in relation to the extension of indication for Phenasen was held.

It was suggested in this meeting that a new Clinical overview section of the dossier summarising the intended submission would be provided to the TGA.

A systematic literature search strategy for literature based submissions prepared by a professional research librarian was submitted. The search strategy was finalised and approved by TGA on 9 October 2012. However, prior to the submission of the Pre-submission Planning Form (PPF), the Literature Based Guideline (LBS) was revised on 27 May 2014. Phebra reviewed all the retrieved literatures (2 to 4 June 2014) and analysed it's suitability as per the agreed inclusion criteria. Phebra did not find any additional literature that could be considered for inclusion in the efficacy section. Some of the published papers were on safety aspects of arsenic trioxide and they were considered for preparing the Risk Management Plan (RMP).

On 24 June 2014, Phebra received an email confirmation that the proposed indication:- '*For the induction of remission and consolidation in patients with previously untreated Acute promyelocytic leukemia (APL) in combination with all-trans retinoic acid (ATRA) and chemotherapy unless ATRA and / or chemotherapy is contraindicated.*' is within the scope of the broader orphan indication '*For the treatment of acute promyelocytic leukemia*'.

Contents of the clinical dossier

Scope of the clinical dossier

The current dossier and application is a Mixed/Hybrid type application (a combination of complete study reports of limited clinical studies carried out and supported with bibliographical references). This application is based on the ALLG Phase II clinical trial (APML4) as the pivotal study supported by the published literatures.

The literature search was performed at 3 different periods. Initial search was performed on 16 to 17 October, 2012 and updated searches in 3 to 4 September, 2013 and in 2 to 4 June 2014, the entire literature search output that was generated was reviewed against the inclusion and exclusion criteria. None of the additional literatures identified in 2 to 4 June 2014 were found suitable for inclusion in the dossier in support of the claimed indication. The sponsors confirm that the search strategy used to generate the search output for the application was in full accordance with the search strategy approved by the TGA.

The submission contained the following clinical information:

- Phase II study (APML4) of clinical efficacy in support of the proposed extended indication for use in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with ATRA and chemotherapy unless ATRA and/or chemotherapy is contraindicated.
- All of the other clinical efficacy data is from published studies, including 4 controlled trials with ATO in combination treatment; 5 open, uncontrolled trials, in combination treatment.; 7 studies using ATO as single agent including, 5 open, uncontrolled trials, with ATO as single agent treatment in adults and 2 in children; 1 meta-analysis of 5 trials and 1 historical control trial, APML3, which is considered the 'control' for APML4 (Table 1).

Table 1: List of clinical studies providing efficacy data

Study Identifier (Author)	Study Design	ATO dose and treatment regimen
As combination treatment		
Lo-Coco et al[3] 2013, module 5.3.5.1.1	RCT, active control, prospective multicentre study, noninferiority	0.15 mg/kg/day intravenously (iv) during induction and consolidation
Shen et al[6], 2004 , module 5.3.5.1.2	RCT, active control, prospective multicentre study	0.16 mg/kg/day iv, during induction and maintenance
Powell et al[5], 2010, module 5.3.5.1.3	RCT, active control, prospective multicentre study	0.15 mg/kg/day iv, for post-remission treatment (prior to consolidation)
Dai et al[4], 2009 module 5.3.5.1.4	Non-randomised, active control, prospective single centre study	10 mg/day iv for 28 days, during induction and for 10-14 days during consolidation/maintenance.
ALLG APML4[1] module 5.3.5.2.1	Open, uncontrolled, prospective multicentre study; in CSR APML3 is active control	0.15 mg/kg/day iv during induction, and intermittent cycles in consolidation
Iland et al[2] 2012, ALLG APML3 module 5.3.5.4.1	Open, uncontrolled, prospective multicentre study - historical control for APML4	No ATO regimen

Table 1 continued List of clinical studies providing efficacy data

Study Identifier (Author)	Study Design	ATO dose and treatment regimen
As combination treatment		
Ravandi et al[7] 2009 module 5.3.5.2.2	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, during both induction and maintenance
Lou et al[8] 2012 module 5.3.5.2.3	Open, uncontrolled, retrospective single centre study	10 mg/day iv, during both induction and maintenance
Pei et al[9] 2012 module 5.3.5.2.4	Open, uncontrolled, prospective single centre study	0.16 mg/kg/day iv, during induction and 10 mg/day iv 10 mg/m2/day iv for 14-21 days in 3rd month during maintenance for 6–8 courses over approximately 3 years
Gore et al[10] 2010 module 5.3.5.2.5	Open, uncontrolled, prospective multicentre study	0.15 mg/kg/day iv, on weekdays from Day 8 for 30 doses. during consolidation only
Meta-analysis		
Wang et al[14] 2011 module 5.3.5.3.1	Meta-analysis – includes 5 trials* in newly diagnosed APL	0.16 mg/kg/day iv in Shen et al 2004, Li et al 2008, and Su et al 2006. 10 mg/day iv in Bai et al 2007 and Wang et al 2004
As single agent treatment		
Ghavamzadeh et al[11] 2006 module 5.3.5.2.6	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days during consolidation. No maintenance treatment was given.
Ghavamzadeh et al[12] 2011 module 5.3.5.2.7	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days during consolidation, for up to 4 courses. Additional consolidation courses at 1 and 2 years
Mathews et al[13] 2006 module 5.3.5.2.8	Open, uncontrolled, prospective single centre study	ATO 10 mg/day iv in induction until CR (to max 60-75 days), 28 days break then, ATO (same dose) for consolidation for 4 weeks, 28 day break, ATO (same dose) as maintenance for 10 days/month, every 4 weeks, for 6 months while subjects remained in remission.
Mathews et al[14] 2010 module 5.3.5.2.9	Open, uncontrolled, prospective single centre study	No treatment – long term follow-up of Mathews et al 2006
Alimoghaddam et al[15] 2006 module 5.3.5.2.10	Open, uncontrolled, prospective study	Induction ATO 0.15 mg/kg/day until CR Consolidation ATO (same dose as induction) for 28 days daily (after a 4 week break, post CR) No maintenance treatment.
As single agent treatment in children		
George et al[16] 2004 module 5.3.5.2.11	Open, uncontrolled, prospective single centre study	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation (Bk), then 6 cycles of maintenance 10 days every month.
Zhou et al[17] 2010 module 5.3.5.2.12	Open, uncontrolled, prospective single centre study	Induction: 0.16 (patients aged above 6 years of age) or 0.20 (patients aged 4 to 6 years of age) mg/kg/day iv, with a maximum daily dose of 10 mg. ATO given daily until Haematological CR or to a maximum of 60 doses, with a 28 days (Bk) then. Maintenance: 14 days every month in 1st year, every 2 months in 2nd year, every 3 months in 3rd year.

'Bk' – indicates a 4 week break after induction when CR achieved, or a 4 week break between consolidation treatment and maintenance.

Of the 5 trials in the meta-analysis, 1 was identified in the literature search and included (Shen et al 2004); but the other 4 were excluded during the literature sorting phase-primarily on the basis of being single trials, reported in Chinese language journals.

Paediatric data

The submission did not include specific clinical studies in paediatric patients and no formal paediatric development plan has been prepared for Phenasen in this proposed indication. However, there is limited clinical data with the use of arsenic trioxide in paediatric population. All trials except Lo-Coco et al (2013)[7] and Gore et al (2010) included adolescent patients (age 14 to 18 years). The APML4 study, Ghavamzadeh et al (2006)[8] and Mathews et al (2006)[9] also included children. Two published papers using ATO as single agent in newly diagnosed APL (George et al, 2004 and Zhou et al, 2010) were conducted only in paediatric (< 12 years) and adolescent patients (12 to 15 years)[10]. Efficacy and safety in paediatric patients below the age of 5 years has not been studied.

Good clinical practice (GCP)

The APML4 study was conducted in compliance with GCP guidelines. All other published studies were also conducted in compliance with Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic data was provided in this submission.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic data was provided in this submission.

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

Dosage selection for the pivotal studies

No new data was submitted.

[7] Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood 2010;116:3171-9.
[8] Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. J Clin Oncol 2011;29:2753-7.
[9] Mathews V, George B, Lakshmi KM, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. Blood 2006;107: 2627-32.
[10] George et al 2004 (11 patients in the age range 6-14) and Zhou et al 2010 (19 patients under 15 years in age).

Efficacy

Studies providing efficacy data

One Phase II study (APML4) of clinical efficacy in support of the proposed extended indication for use in patients with previously untreated APL in combination with ATRA and chemotherapy unless ATRA and/or chemotherapy is contraindicated as well as published studies, including 4 controlled trials with ATO in combination treatment; 5 open, uncontrolled trials, in combination treatment.; 7 studies using ATO as single agent including, 5 open, uncontrolled trials, with ATO as single agent treatment in adults and 2 in children; 1 meta-analysis of 5 trials and 1 historical control trial, APML3, which is considered the 'control' for APML4 (Table 1).

Evaluator's conclusions on clinical efficacy

> ***for 'remission and consolidation in patients with previously untreated Acute promyelocytic leukaemia (APL) in combination with all-trans retinoic acid (ATRA) and chemotherapy unless ATRA and/or chemotherapy is contraindicated'.***

A total of 1214 patients in the individual studies (including APML4 and the published studies) were exposed to ATO (with or without ATRA) as part of their study regimen while 458 patients received ATRA alone (controlled trials). All the studies were conducted in newly diagnosed, previously untreated APL patients with genetic diagnosis of APL established by detection of the PML-RARα fusion gene (by RT-PCR assay), demonstration of the t(15;17) translocation (by means of conventional karyotyping or fluorescence in situ hybridization (FISH)). The published studies (pivotal and supportive studies) have mainly been conducted in China or India. The pivotal clinical study, APML4, was conducted in Australia and New Zealand.

ATO as combination treatment in newly diagnosed, previously untreated APL

Nine of the studies summarised individually in Attachment 2 included ATO as part of a combination treatment regimen with ATRA. Not all treatment regimens were the same and only 3 studies compared the combination of ATO + ATRA to ATRA alone during induction (Lo-Coco et al., 2013, Shen et al, 2004 and Dai et al, 2009). The APML4 study was compared to the APML3 study (Iland et al, 2012) as the main difference between the trials was the addition of ATO in APML4 although interpretation was limited due to exploratory nature of analysis and some difference in the duration and dosage of 6MP and MTX that were administered during maintenance therapy in the APML3 and APML4 trials. Two studies included ATO only after remission was achieved, in the consolidation phase (Powell et al, 2010 and Gore et al, 2010); while the studies reported by Dai et al (2009), Lou et al (2013) and Pei et al (2012) included substantial chemotherapy (CT) during the consolidation phase. Overall, 913 patients were treated with ATRA+ATO, 458 patients treated with ATRA alone and 20 patients with ATO alone in the combination treatment studies; this sample was adequate to assess efficacy and safety of ATO used in combination with ATRA for the proposed new indication in newly diagnosed, previously untreated APL.

In APML4 study as well as all other published literature, patients irrespective of risk (Sanz risk classification)[11] were included. The only exceptions were Lo-Coco et al 2013 and Alimoghaddam et al 2006 which included only low-intermediate risk patients. Furthermore, patients who had significant arrhythmias, electrocardiogram (ECG) abnormalities or neuropathy; other cardiac contraindications for intensive chemotherapy

[11]Patients with APL may be stratified into three risk categories on the basis of white blood cell (WBC) count and platelet count. Low risk is a WBC count < $10x10^9$/L and a platelet count > $40x10^9$/L; intermediate risk is a WBC count < $10x10^9$/L and a platelet count < $40x10^9$/L; high risk is a WBC count > $10x10^9$/L.

(left ventricular ejection fraction (LVEF) <50%) were excluded from the Lo-Coco et al 2013 study. Dai et al, 2009 excluded patients with dysfunction of liver or kidney; any heart diseases or cardiac functional insufficiency. Ravandi et al, 2009 excluded patients who had pretreatment QTc[12] interval of > 480 ms. Ghavamzadeh et al 2006 and Ghavamzadeh et al 2011[13] excluded patients with severe renal, hepatic or cardiac dysfunction (creatinine > 2 mg/dl, bilirubin> 5 mg/dl, and ejection fraction <50%). It is important to note that majority the patients in the APML4 pivotal combination study had Eastern Cooperative Oncology Group Performance Status (ECOG PS)[14] of 0 or 1 (87%) while ECOG PS status was not provided for the other 2 pivotal studies (Lo Coco et al, 2013 and Dai et al, 2009).

In the analysis of the APML4 study informal comparisons with the historical APML3 maintenance cohort indicated considerable improvements in Time to relapse (TTR), Disease-free survival (DFS), Overall survival (OS) and Event-free survival (EFS) with the addition of ATO to the standard ATRA plus CT regimen. However, these results should be interpreted with caution due to the post hoc, exploratory nature of the analysis and certain differences in treatment regimens in the APML4 and APML3 studies. However, results from this Phase II open-label study did demonstrate that induction and consolidation treatment with ATO with ATRA/CT results in CR of 95% at end of induction with median time to relapse of only 53 days and observed annual relapse-free rates of 97.3% at 1 and 2 years and 95.4% at 3, 4 and 5 years. Furthermore, use of ATO in the consolidation cycle enabled reduced exposure to CT as it substituted idarubicin (IDA) (which was used in Study APML3).

The study by Lo-Coco et al, (2013) showed that a combination of ATRA and ATO given for induction and consolidation therapy is at least not inferior and is possibly superior to standard ATRA and anthracycline based CT for adults with newly diagnosed, low to intermediate risk APL. The observed advantage in the 2 year EFS (which was primary efficacy endpoint) with ATRA + ATO compared to ATRA +CT (97% versus 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-leukemic efficacy. The study reported Complete Remission (CR) in all (100%) ATRA+ATO patients after a median 32 days of induction.

Dai et al (2009) reported high rates of Relapse free survival (RFS), with combination treatment, while patients receiving ATRA alone had significantly higher relapse rates and lower RFS. The estimated OS of 85% reported by Ravandi et al (2009; with a median 99 weeks follow up) was in line with the results from other studies.

[12] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate in an obvious way (the faster the heart rate the shorter the R-R Interval and QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia to give QTc.

[13] Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. J Clin Oncol 2011;29:2753-7.

[14] Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

In Shen et al, (2004) and Dai et al, (2009) the combination of ATRA + ATO during induction allowed CR to be achieved more quickly (statistically significantly in Dai et al 2009), although there was not a significant difference in the proportion of patients achieving CR. This comparative reduction in median time to achieve CR was also confirmed by the results of APML3 and APML4 (Table 2 below).

Table 2: Number and proportion of subjects achieving CR, median time to CR

	Lo-Coco et al (n=79)	Shen et al Group 1 (n=20)	Dai et al Group A (n=72)	APML3 (n=101)	Lo-Coco et al (n=77)	Shen et al Group 3 (n=21)	Dai et al Group B (n=90)	APML4 (n=124)
Induction Treatment	**ATRA**				**ATRA + ATO**			
Number Achieving CR (%)	75 (95.0)	19 (95.0)	65 (90.3)	91 (90.1)	77 (100.0)	20 (95.2)	84 (93.3)	118 (95.2)
Median Days to CR (range)	35 (26-63)	40.5 (25-65)	39 (25-62)	-	32 (22-68)	25.5 (18-35)	31 (18-59)	53 (34-83)

* APML3 is considered to be the control group (ATRA) for APML4 – together they are presented as a 'controlled trial'

The uncontrolled trial Ravandi et al (2009) reported CR achieved in a median of 28 days, confirming that achievement of CR after combination treatment with ATRA + ATO is rapid.

DFS, RFS or EFS and OS and relapse rates were reported for most studies and are summarised in Table 3 below:

Table 3: Comparison of primary efficacy outcomes in studies with ATRA+ATO

Study Identifier (Author)	Group	Relapses n (%)	DFS %	RFS %	EFS %	OS %
Lo-Coco et al[3] 2013, module 5.3.5.1.1	ATRA	5 (6% 2y)	90.0 (2y)	-	85.0 (2y)	91.0 (2y)
	ATRA + ATO	2 (1% 2y)	97.0 (2y)	-	97.0 (2y)	99.0 (2y)
Shen et al[6], 2004 , module 5.3.5.1.2	ATRA	5 (26.3)	13 mth	-	-	-
	ATRA + ATO	0	20 mth	-	-	-
Powell et al[5], 2010, module 5.3.5.1.3	ATRA	-	70.0	-	63.0	81.0 (3y)
	ATRA+ ATO	-	90.0	-	80.0	86.0 (3y)
Dai et al[4], 2009 module 5.3.5.1.4	ATRA+ ATO	1 (5.0)	-	93.8	-	-
	ATRA	10 (22.2)	-	72.4	-	-
	ATRA+ ATO	4 (4.8)	-	92.6	-	-
ALLG APML4[1] module 5.3.5.2.1	All patients ATRA+ ATO	5	97.0 (2y) 95.0 (5y)	-	§92.0 (2y) 90.0 (5y)	94.0 (2y) 94.0 (5y)
Ravandi et al[7] 2009 module 5.3.5.2.2	All patients ATRA+ ATO	3 (4)	-	-	-	85.0 (99 wk*)
Lou et al[8] 2012 module 5.3.5.2.3	Low risk	5 (4)	-	87.9	-	97.4 (5y)
	High risk	-	-	98.7	-	98.9 (5y)
Pei et al[9] 2012 module 5.3.5.2.4	ATRA + ATO	-	100.0 (5y)	-	-	100.0 (5y)
Gore et al[10] 2010 module 5.3.5.2.5	All patients	-	88.7	-	76.0	88.0 (3y)

* Median follow-up was 99 weeks at publication. § EFS alternative definition

Comments: The above table from the sponsor's Clinical summary had errors in reporting results of the Lou *et al*, 2013 study. A question regarding this has been included under *Clinical questions* in this report.

The study reported by Powell et al (2010) involving 481 patients with newly diagnosed APL shows that addition of As_2O_3 to consolidation therapy to regimens using ATRA and anthracycline based CT improves EFS. Gore et al (2010) has shown similar results as those reported by Powell, substituting a consolidation cycle of CT for ATO. However, both these studies did not use ATO for remission induction although the proposed indication suggests use of ATO for induction and consolidation in newly diagnosed APL.

Overall, there was adequate evidence to support use of ATO in combination with ATRA and/ or CT in newly diagnosed, previously untreated patients with APL.

However, there are several unanswered questions such as:

- ***The optimal timing for the As2O3 therapy in the overall treatment regimen:*** The proposed dosing regimen for ATO as combination therapy for newly diagnosed APL was used in the 3 pivotal studies (APML4 study. Lo Coco, 2013 and Dai, 2009). Results from the large study involving 481 newly diagnosed patients with APL (Powell, 2010) demonstrated that As_2O_3 given as initial consolidation therapy is safe and improves event-free, disease-free and overall survival for newly diagnosed patients with APL. Similar results were observed in Gore et al 2010. However, both studies did not use As_2O_3 for remission induction.
- ***The best approach to decrease early deaths especially in patients with high risk disease (WBCs>10x109/L) and the role of cytarabine in APL***: The APML4 study included 19% of patients with high risk and the Powell study included 23% of patients with high risk. Lo Coco, 2013 excluded patients with high risk and baseline risk was not provided in Dai, 2010, Shen, 2004 studies. In one published study (Pei, et al, 2012), 16 of the 73 patients with newly diagnosed APL had white blood cell counts (WBC) >$10x10^9$/L and received CT plus cytarabine, plus results in these patients was not provided. The APML4 study also used mandatory steroids (10 mg prednisone) during first 10 days of induction therapy and aggressive platelet support to meet haemostatic targets which helped to reduce early deaths due to APDLS. Similar supportive treatment has been proposed for the proposed new indication.
- ***The choice of anthracycline to be used in combination with ATO is not specified***. IDA was used in studies APML4 and Lo Coco, 2013 but DA was used in studies published by Dai (2009), Shen (2004) and Powell (2010).

ATO as single agent treatment in newly diagnosed, previously untreated APL

The 6 studies with ATO single agent treatment identified in the literature search provided data on 281 patients with newly diagnosed APL (including 30 children aged <15 years) exposed to single agent treatment with ATO. The proportion of patients achieving CR was approximately 86% in both the interim report (82/94, Ghavamzadeh, 2006) and the long-term follow-up (169/197; Ghavmazadeh, 2011) with median time to CR of 30 days in both studies. The main reason for failure of ATO therapy was early mortality during remission induction phase mainly due to APL differentiation syndrome, cerebral haemorrhage and cardiac arrest (Ghavamzadeh, 2006). In the long-term report (Ghavmazadeh, 2011), early death and remission failure were more common among patients with WBC counts greater than 10 x 109/L compared with those with lower counts (42% versus 6%; P = 0.001), while mortality during induction was higher in patients with platelet counts < 40 x 10^9/L as compared with platelet counts > 40 x 10^9/L (20% versus 8%; P = 0.11). The increased number of courses of ATO increased DFS but had no significant effect on OS. The 2 reports by Matthews (2006 and 2010) following ATP monotherapy induction and consolidation treatment showed similar results with CR of about 86% and better response in patients with low/ intermediate risk compared to those with high risk at baseline. Two studies (George, 2004 and Zhou 2010) in 30 paediatric patients (aged < 15years) provided some preliminary evidence for efficacy of ATO monotherapy in newly diagnosed APL but this needs to evaluated further due to risks of early mortality during remission induction phase as well as unknown long-term risks associated with arsenic trioxide (hepatotoxicity, secondary cancers).

Overall results of above studies suggest that ATO may provide a better risk benefit profile for certain newly diagnosed adult patients with APL. There were no direct comparisons of ATO monotherapy against ATRA based and other chemotherapy regimens in newly

diagnosed patients but this is not a limitation of the submission since sponsors proposed use of ATO monotherapy only in newly diagnosed APL when ATRA and/ or chemotherapy is contraindicated. However, due to risk of early mortality during remission induction phase with ATO treatment, it is important to determine the subgroups of patients likely to benefit from ATO monotherapy. It appears that patients at low/intermediate risk showed better results compared to those with high risk and this was shown in both Ghavmazadeh 2011 and Matthews, 2006 reports. Good outcomes to treatment with ATRA and anthracycline based CT can be achieved but for some patient groups CT may be considered too toxic (in some countries ATRA and CTs may not be widely available/affordable). ATO monotherapy may also be beneficial in patients who may not be able to tolerate complex treatment plans, toxicities including myelosuppression associated complications and cardiotoxicity. The sponsors proposed that ATO be used as single agent therapy in newly diagnosed APL in patients in whom ATRA and/or chemotherapy is contraindicated. However, the patients evaluated in the six monotherapy studies did not represent this target patient population (2 of 6 studies included only paediatric patients aged 4 to 15 years and median age of patients in other studies was only 28 to 30 years). Patients with contraindications to ATRA and/ or chemotherapy are more likely to be elderly patients with comorbidities but these patients were not evaluated in any of the submitted single agent ATO studies. Overall, the evidence for efficacy and safety of use of ATO as single agent in newly diagnosed APL is inadequate.

The dose of ATO used in most of the published clinical studies was fairly consistent, either a dose of 0.15 or 0.16 mg/kg body weight (for a 70 kg patient 10.5 mg/day) or a 10 mg per day dose. The dose of ATO was reduced in cases of toxicity (arsenic related QTc interval prolongation and possible arrhythmias, Grade 3 to 4 haematological and hepatic toxicity).

Persistence of efficacy and/or tolerance: The effectiveness of ATO throughout the induction, consolidation and maintenance cycles does not appear to change or diminish over time and with repeated exposure. The duration of follow-up in APML4 study was 3-5 years, while that in other combination studies ranged from 2 years to 5 years. The published ATO monotherapy studies by Mathews et al, 2010 and Ghavamzadeh et al 2011 provide longer term follow-up of patients, providing up to 5 year data. However, interpretation from these studies was limited as this longer term follow-up does not describe dosage beyond the maintenance treatment that was planned. In some studies (such as Ghavamzadeh et al 2006, Wang et al 2011), it was common to repeat an induction cycle and continue treatment in patients who relapsed.

Safety

Studies providing safety data

In the pivotal efficacy studies (APML4, Lo-Coco et al 2013 and Dai et al, 2009), the following safety data were collected:

All patients who received any dose of study drug (ATO or ATRA) were monitored throughout their participation in the study and included in the safety population analysis. Each study site's local laboratory performed haematology, biochemistry and coagulation assessments of samples taken throughout the study. All other study related procedures were performed at the study site, and the results were assessed by the appropriate study site personnel. These included: Oxygen saturation (arterial), Body weight, Height, chest X-Ray, ECG (QTc interval), LVEF, Vital signs (pulse, respiration, body temperature, blood pressure), pregnancy testing, bone marrow (BM) aspirate for cytogenetics.

Comments: Although included in the protocol, pulse, respiration and blood pressure were not included in the case report form (CRF) of the APML4 pivotal study.

All AEs that occurred while a patient was receiving treatment (study drugs) on the trial were recorded in the CRFs, including the nature of the event and a toxicity grading using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The causal relationship[15] to treatment (attribution of causality), as assessed by the Investigator was also recorded, with the temporal relation between the adverse event (AE) and the study drugs included in the documentation being considered as decisive in attribution. All serious AEs (SAEs) that occurred while receiving treatment and within 30 days of the last dose of a study drug as treatment, were required to be reported16. Local Independent Ethics Committees (IECs) were also required to be notified of SAEs according to institutional guidelines.

Dose-response and non-pivotal efficacy studies

Brief description of safety/ toxicity findings were provided in most of the published studies included in the submitted dossier.

Comments: As this submission is a hybrid literature based submission with the clinical data coming from published clinical studies using a number of different 'study products' (ATO), no formal safety evaluation plan or integrated narrative is available. However, a brief description of the safety data available from each of the individual studies is provided. Drug concentration data (whole blood arsenic levels) were not available for any of the studies with exception of 2 single agent studies (Matthews et al, 2010 and Zhou et al, 2010).

Patient exposure

A total of 1214 patients in the individual studies (including APML4 and the published studies) were exposed to ATO (with or without ATRA) as part of their study regimen, while 458 patients received ATRA alone (controlled trials).

In the combination treatment studies, 913 patients were treated with ATRA+ATO, 458 patients treated with ATRA alone and 20 patients with ATO alone (Table 4). Overall, 281 patients with newly diagnosed APL (including 30 children aged <15 years) were exposed to single agent treatment with ATO (Table 5).

[15] The following definitions of the causality to treatment were used:
- Definite: The AE is clearly related to treatment/study drug
- Probable: The AE is likely related to treatment
- Possible: The AE may be related to treatment
- Unlikely: The AE is doubtfully related to treatment
- Unrelated: The AE is clearly NOT related to treatment

[16] All SAEs considered by the site investigator to be related to ATO or for which a causal relationship to ATO could not be ruled out, were also to be faxed immediately to Phebra. Once an SAE had resolved, a follow-up SAE report was required to be faxed to the Trial Centre (and Phebra if ATO was implicated).

Table 4: Patient exposure in combination treatment studies

(Author)	ATRA (or no ATO)	ATRA + ATO	ATO	regimen
As combination treatment				
Lo-Coco et al[3] 2013, module 5.3.5.1.1	79	77	0	0.15 mg/kg/day iv, during induction and consolidation
Shen et al[6], 2004 , module 5.3.5.1.2	20	21	20	0.16 mg/kg/day iv, during induction and maintenance
Powell et al[5], 2010, module 5.3.5.1.3	237	244	0	0.15 mg/kg/day iv, for post-remission treatment (prior to consolidation)
Dai et al[4], 2009 § module 5.3.5.1.4	52	110	0	10 mg/day iv, during induction and consolidation/maintenance.
ALLG APML4[1] 4 module 5.3.5.2.1	0	124	0	0.15 mg/kg/day iv during induction, and intermittent cycles in consolidation
Jlland et al[2] 2012, *ALLG APML3*	*70*	*0*	*0*	*No ATO regimen – the maintenance cohort (total study n=101)*
Ravandi et al[7] 2009 module 5.3.5.2.2	0	82	0	0.15 mg/kg/day iv, during both induction and maintenance
Lou et al[8] 2012 Module 5.3.5.2.3	0	137	0	10 mg day iv, during both induction and maintenance
Pei et al[9] 2012 module 5.3.5.2.4	0	73	0	0.16 mg/kg/day iv, during induction and 10 mg/day iv for 14-21 days in 3rd month during maintenance for 6–8 courses over approximately 3 years
Gore et al [10]2010 module 5.3.5.2.5	0	45	0	0.15 mg/kg/day iv, on weekdays (30 doses) from Day 8, during consolidation
Sub total	**458**	**913**	**20**	
§Dai: from 72 patients in Group A receiving only ATRA, 20 received ATO in Group A1 in addition to the 90 patients initially exposed in Group B				

Table 5: Patient exposure in single-agent studies

Study Identifier (Author)	Patients Exposed			ATO dose and treatment regimen
	ATRA (or no ATO)	ATRA + ATO	ATO	
As single agent treatment				
Ghavamzadeh et al[11]2006 module 5.3.5.2.6	0	0	94	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days consolidation.
Ghavamzadeh et al[12]2011 module 5.3.5.2.7	0	0	+ 68 (in addition to 111† in 2006 paper)	0.15 mg/kg/day iv, for induction (Bk), and 6 days/week for 28 days consolidation. Additional consolidation courses at 1 and 2 years
Mathews et al[13] 2006 module 5.3.5.2.8	0	0	72	10 mg/day iv, during induction (Bk), 28 days daily for consolidation, then 6 cycles of maintenance 10 days every month.
Mathews et a[14] 2010 module 5.3.5.2.9	0	0	(no additional)	No treatment – long term follow-up of Mathews et al 2006
Alimoghaddam et al[15] 2006 module 5.3.5.2.10	0	0	17	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation. No maintenance.
As single agent treatment in children				
George et al[16] 2004 module 5.3.5.2.11	0	0	11	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation (Bk), then 6 cycles of maintenance 10 days every month.
Zhou et al[17] 2010 module 5.3.5.2.12	0	0	19	0.15 mg/kg/day iv, during induction (Bk), 28 days daily for consolidation (Bk), then maintenance 14 days every month in 1st year, every 2 months in 2nd year, every 3 months in 3rd year.
Single agent total	**0**	**0**	**281**	*†While 111 patients were reported in the paper published in 2006, only 94 were newly diagnosed. Bk indicates a break in treatment (between cycles)*
Total	**458**	**913**	**301**	

Comments: The exposure was adequate to evaluate the adverse event profile of Phenasen for the proposed indication for treatment of newly diagnosed APL patients as combination therapy (with ATRA/CT). However, the studies for ATO monotherapy were not conducted in newly diagnosed patients with contraindications to ATRA and/or CT and the published studies only provided brief description of safety data.

In the pivotal Phase II open-label study APML4, 124 patients commenced induction treatment and were evaluable for safety analysis. All 124 patients received both ATRA and ATO; the maximum exposure for patients to ATO would be 81 days over the induction (IND) and 2 cycles of consolidation therapy (CON1 and CON2). Although 112 patients completed these 3 courses, patients did not all receive the full protocol prescribed dose (particularly during IND), although close to 50% received between 90 and 100% of the protocol prescribed dose (60/124, 48% in IND; 59/112, 53% in CON1 and CON2).

Comments: The dose of ATO prescribed in this study is the same as that approved for use in patients with relapsed APL. Additionally, the total exposure is similar to that recommended in the product information for Phenasen (ATO) in relapsed APL (60 days for induction and 25 days for consolidation, total 85 days refer to Phenasen PI). Drug concentration data (whole blood arsenic levels) were not available.

Safety issues with the potential for major regulatory impact

Liver toxicity

Hepatotoxicity was quite common following ATO treatment of newly diagnosed patients with APL, when used in combination with ATRA as well as single agent treatment. However, most cases of hepatotoxicity were managed with supportive care, ATO dose reduction, temporarily withholding ATO treatment or a combination of these options.

Haematological toxicity

Hyperleukocytosis was very common and managed with hydroxyurea during most studies. In some studies hyperleukocytosis was related to poor outcomes. Low platelet counts were associated with higher risk of early death during ATO induction treatment phase. However, aggressive monitoring of haematological function and supportive treatment with platelet infusions and so on may help to reduce adverse outcomes associated with ATO related haematological toxicity.

Cardiovascular safety

Prolongation of QTc interval was quite common following ATO treatment of newly diagnosed patients with APL; both when used in combination with ATRA as well as single agent treatment. However, this could be managed with a 12-lead electrocardiogram performed at baseline and weekly during induction and consolidation therapy as well regular monitoring and correction of electrolyte abnormalities in patients receiving ATO therapy.

Postmarketing data

Arsenic trioxide is available in the USA since 2000 and in Europe since 2002. It has been available on the Australian market since 1998 (SAS) and as registered medicinal product in Australia from May 2009. All patients treated with Phenasen in the clinical study were evaluated for safety during the study and at follow-up. Safety assessments were based on physical examination, vital signs (heart rate, blood pressure, respiration rate, and temperature), ECG, clinical laboratory measures and interviews for subjective complaints.

In Australia, 90.71 patient years of Phenasen use has been estimated since its initial registration (7 May 2009 to 6 May 2014). The sponsor has submitted 3 Periodic Safety Update Reports (PSURs) so far (Table 6).

Table 6: Summary of PSURs completed and submitted for Phenasen

PSUR No.	Date of PSUR	Data Lock Point	[redacted]	Patient years represented	No. of AEs reported§
PSUR#1	5 Aug 2010	6 May 2010		14.14	12
PSUR#2	4 Jul 2011	6 May 2011		18.44	0
PSUR#3	2 Jul 2012	6 May 2012		18.93	1

§ Does not include AEs identified in the published literature (1 paper each in PSUR#1and PSUR#2 and 3papers in PSUR#3)

It is noted that within the PSUR#1 SAEs from the APML4 clinical study that were considered possibly or probably related to Phenasen (ATO) were reported to Phebra. Additionally, 2 of the 3 published studies included in PSUR#3 have been included as supportive studies in this submission (Ghavamzadeh et al, 2011 and Alimoghaddam, 2006).

NB: The number of vials sold has been deleted (using a black box) from this table.

The TGA Database of Adverse Events Notifications (DAEN) was searched for Phenasen (ATO) and arsenic trioxide between 1 January 2001 and 17 April 2014 (report searched on 31 July 2014)). Only 4 reports (cases) had been reported. Out of these 4 reports, only one report had an outcome of death and it was suspected to be related to Phenasen (including nervous system disorder and systemic mycosis). The adverse events reported in the first PSUR were: neutropenia, febrile neutropenia, diarrhoea, QTc prolongation, ventricular tachycardia, fatigue, alkaline phosphatase elevation, elevation of liver enzymes, palpitations, chest pain and peripheral oedema. In the second PSUR, the adverse events reported were: hyperleukocytosis, APLDS and renal insufficiency. In the third PSUR, one serious, unexpected (but not related) adverse event of 'stroke like episode' was received by Phebra from a physician. Three scientific literature articles were cited which reported serious adverse events of APLDS differentiation syndrome, cardiac toxicity, liver toxicity, renal toxicity intracranial haemorrhage and pulmonary fungal infection. All these adverse events, except for pulmonary fungal infection, have been observed in previous studies and are listed in the currently approved Phenasen Injection PI. No adverse event reports were received by Phebra during the period 7 May 2012 till 31 July 2014.

Evaluator's conclusions on safety

The demographic data for the patients in the APML4 trial, the APML3 maintenance cohort and other published studies were generally similar and consistent with the expected target patient population of newly diagnosed APL (Table 7). For the majority of the published studies, only brief description of safety results were available; AEs were not reported or analysed in terms of the Medical Dictionary for Regulatory Activities (MedDRA) system[17], organ and class and it was not possible to analyse the AEs across all studies.

[17] In the late 1990s, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed MedDRA, a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans.

Table 7: Demographic data and baseline characteristics of the groups treated with ATO in combination with ATRA

Characteristic	Lo-Coco (n=77)	Shen (n=21)	Powell (n=244)	Dai (n=104, Groups B, A1)	APML4 (n=124)	Ravandi (n=82; All)	Lou (n=137; All)	Pei (n=73)	Gore (n=45)
Age, years median (range) Age group No.(%) 15-60 >60	44.6 (19.1-70.2)	34 (14-62)	 207 (85) 37 (15)	B: 32 (14-67) A1: 29 (16-62)	44 (3-78)	47 (14-81) 23 (28)	38.4 (13-77) 4 (2.9)	37 (14-72)	50 (19-70)
Gender No. (%) Male Female	 40 (52) 37 (48)	 12 (57) 9 (43)	 123 (50) 121 (50)	 65 (59) 45 (41)	 62 (50) 62 (50)	 44 (54) 38 (46)	 73 (53.3) 64 (46.7)	 42 (58) 31 (42)	 - -
WCC, $x10^9/L$	1.5 (0.3-10.0)	-	-	-	2.4 (0.1-85.8)	2.5 (0.4-195.0)	-	2.3 (0.6-62.6)	-
Platelet $x10^9/L$	31 (3-224)	-	-	-	22 (2-173)	32 (7-261)	-	23 (5-138)	-
Risk, No. (%) Low Intermediate High	 33 (43) 44 (57) 0	 - - -	 - - -	 - - -	 33 (26) 67 (54) 23 (19)	 26 56	 - - 45	 - - -	 (36) (29) (32)
FLT3 mutation No./Total No. (%)	14/65 (22)	-	-	-	52 (44)	-	-	-	-

Safety of ATO as combination therapy with ATRA/CT in newly diagnosed APL

The AE profile observed in newly-diagnosed patients with APL was similar to the known AE profile of ATO in relapsed ATO and no new or unexpected AEs were identified. The common AEs (>1% incidence) reported in the Randomised controlled trial (RCTs) is summarised in Table 8. The safety results reported in the RCTs confirmed the expected AE profile as patients receiving ATRA alone or ATRA + CT had more frequent prolonged cytopenias, mucositis and infections, while groups given ATRA + ATO had more frequent prolonged QTc and liver function abnormalities (Lo-Coco et al, 2013, Shen et al, 2004). All studies in newly diagnosed, previously untreated patients with APL reported early deaths most often during induction treatment with lower incidence during consolidation/ maintenance phases (Table 9).

Table 8: Common AEs reported in RCT (occurring in ≥1 % of patients)

Study Identifier (Author)	Adverse Events	No. of Patients (%)		
		ATO	ATO + ATRA	ATRA or ATRA+CT
Lo-Coco et al[3] 2013, module 5.3.5.1.1	§ n=68 †n=69		*(n=77)*	*(n=79)*
	Haematologic:			
	Gr 3 or 4 neutropenia and/or		35 (46)	62 (79)
	Thrombocytopenia (>15 days),		45 (59)	70 (88)
	Hyperleukocytosis		35 (47)	19 (24)
	Non-haematologic:			
	Hepatic (Grade 3 or 4)		43 (63)§	4 (6)†
	Prolonged QTC interval		12 (16)	0
Shen et al[6], 2004 , module 5.3.5.1.2		*(n=20)*	*(n=20)*	*(n=21)*
	Haematologic:			
	Hyperleukocytosis	12 (67)	14 (70)	10 (53)
	Non-haematologic:			
	Hepatic (Grade 3 or 4)	2 (10)	2 (10)	1 (5)
	Dry mouth	2 (11)	12 (60)	11 (58)
	Headache	1(6)	2 (10)	4 (21)
Powell et al[5], 2010, module 5.3.5.1.3			*(n=244)*	*(n=237)*
	Haematologic			
	Grade 3		(21)	(16)
	Grade 4		(54)	(67)
	Non-haematologic			
	Grade 3		(41)	(30)
	Grade 4		(5)	(5)
	Headache (Grade 3)		(7)	(3)
	Nausea (Grade 3)		(4)	(3)
	Electrolyte abnormalities (Grade 3)		(3)	(1)
Dai et al[4], 2009 module 5.3.5.1.4			*(n=90)*	*(n=72)*
	Haematologic:			
	Hyperleukocytosis		'common'	'common'
	Non-haematologic:			
	Hepatotoxicity: Total		56 (62)	14 (19)
	Grade 1		33(37)	8(11)
	Grade 2		15 (17)	4(6)
	Grade 3		7(8)	2(3)
	Grade 4		1(1)	0
	Dry lips		41 (46)	30 (42)
	Headache		18 (20)	13 (18)
	Skin reaction		14 (16)	10 (14)
	Fluid retention		21 (23)	5 (7)
	Differentiation Syndrome		3 (3)	2(3)

Table 9: Deaths on treatment in RCTs

Study Identifier (Author)	Early deaths during induction	Deaths during consolidation	Deaths during maintenance
Lo-Coco et al, 2013	4	4	8 (at 24 months)
ATRA + CT	4	3	7
ATO	0	1	1
Shen et al, 2004	4	N/A	2
ATRA + CT	1		
ATRA + ATO	1		
ATO	2		
Powell et al, 2010	-	-	38 (19 each group)
Dai et al, 2009	12 (both groups)§	-	-
ALLG APML4	4	-	3
§ 7 from group A and 6 from group B did not enter consolidation; 12 were early deaths			

Safety results of pivotal Study APML4

There were 7 deaths of which 4 were early deaths during induction period. Two of the early deaths were caused by intracerebral haemorrhage, with other causes of death reported as: myocardial ischaemia, cerebral oedema, infection (2 deaths due to *Klebsiella pneumonia*) and progressive AML. Overall, 91 of the 124 patients commencing induction treatment (73%) experienced SAEs. Of the 91 patients, 63 (69%) experienced more than 1 SAE; 1 patient experienced 11 SAEs. The most common SAEs were: reduced neutrophils/granulocytes, febrile neutropenia, elevated liver function tests and infection (with Grade 3 or 4 neutrophils) occurring in more than 10% of patients. Elevated Gamma-glutamyl transpeptidase (GGT), prolonged QTc interval and APLDS occurred in more than

5% of patients. In general, consolidation was associated with considerably less toxicity than induction, and this was especially evident for hepatic, gastrointestinal, infective, and metabolic AEs. No APLDS was observed in consolidation phase. Compared with the first cycle of consolidation, biochemical hepatotoxicity and infections were also less frequent in the second cycle when ATO and ATRA were given on an intermittent schedule (weekdays only for ATO and alternate weeks for ATRA) (Table 10).

Table 10: Adverse events reported by worst grade in IND and CON

		Induction		Consolidation 1		Consolidation 2	
Adverse Event	**Grade**	***N***	**% of 121**	***N***	**% of 112**	***N***	**% of 111**
Cardiac							
Conduction abnormality	1	2	2	2	2	1	1
Supraventricular arrhythmia	0	96	79	93	83	100	90
	1	18	15	15	13	9	8
	2	6	5	4	4	2	2
	3	1	1	0	0	0	0
Ventricular arrhythmia	1	3	2	0	0	0	0
	2	0	0	1	1	0	0
	4	0	0	1	1	0	0
Left ventricular systolic dysfunction	1	0	0	1	1	0	0
	2	1	1	1	1	1	1
Prolonged QTc	1	29	24	24	21	26	23
	2	33	27	35	31	26	23
	3	17	14	10	9	5	5
Hepatic/Metabolic							
Bilirubin	1	18	15	4	4	2	2
	2	7	6	1	1	0	0
	3	7	6	0	0	0	0
GGT	1	23	19	28	25	14	13
	2	35	29	10	9	5	5
	3	41	34	9	8	1	1
	4	3	2	0	0	0	0
ALT/AST	1	33	27	39	35	23	21
	2	33	27	10	9	3	3
	3	28	23	6	5	0	0
	4	2	2	0	0	0	0
Liver dysfunction	2	1	2	1	1	0	0
	3	1	2	0	0	0	0
	4	1	1	0	0	0	0
Hyperglycaemia	1	16	13	13	12	10	9
	2	18	15	5	5	2	2
	3	7	6	1	1	1	1
	4	2	2	0	0	0	0
Neurology/Pain							
Dizziness	1	13	11	8	7	4	4
	2	8	7	0	0	0	0
Mood alteration	1	13	11	5	4	4	4
	2	11	9	0	0	2	2%
	3	2	2	1	1	0	0
Pain, musculoskeletal	1	14	12	12	11	6	5
	2	9	7	5	5	2	2
	3	3	2	0	0	0	0

Table 10 continued: Adverse events reported by worst grade in IND and CON

		Induction		Consolidation 1		Consolidation 2	
Adverse Event	Grade	N	% of 121	N	% of 112	N	% of 111
Pain, head headache	1	37	31	19	17	17	15
	2	28	23	16	14	7	6
	3	4	3	1	1	0	0
Seizures	2	0	0	0	0	0	0
	3	1	1	0	0	0	0
Gastrointestinal							
Nausea	1	33	27	25	22	28	25
	2	32	26	9	8	1	1
	3	9	7	1	1	0	0
Vomiting	1	23	19	13	12	8	7
	2	19	16	6	5	3	3
	3	4	3	0	0	0	0
Diarrhoea	1	41	34	13	12	8	7
	2	28	23	1	1	6	5
	3	12	10	2	2	1	1
Mucositis	1	8	7	5	4	3	3
	2	50	41	2	2	0	0
	3	16	13	0	0	0	0
	4	1	1	0	0	0	0
Haematological							
Thrombosis/thrombus/embolism	2	9	7	4	4	1	1
	3	7	6	7	6	2	2
	4	1	1	0	0	1	1
CNS haemorrhage	1	1	1	0	0	0	0
	2	2	2	0	0	0	0
Haemorrhage, GI	1	15	12	0	0	0	0
	2	3	2	0	0	1	1
	3	5	4	0	0	0	0
Haemorrhage, pulmonary	1	15	12	1	1	1	1
	2	5	4	0	0	0	0
	3	5	4	0	0	0	0
	4	2	2	0	0	0	0
Platelets	1	0	0	15	13	8	7
	2	0	0	1	1	0	0
	3	7	6	0	0	0	0
	4	114	94	0	0	0	0
Neutrophils	1	0	0	7	6	12	11
	2	0	0	15	13	22	20
	3	0	0	42	38	27	24
	4	121	100	27	24	3	3
Infection							
Febrile neutropenia	3	47	39	6	5	0	0
	4	3	2	0	0	0	0
Infection (documented clinically)	2	11	9	3	3	12	11
	3	55	45	10	9	3	3
	4	2	2	1	1	1	1
Dermatological							
Rash	1	31	26	10	9	10	9
	2	31	26	5	4	6	5
	3	4	3	0	0	0	0
	4	1	1	0	0	0	0
Pruritis	0	98	81	105	94	106	95
	1	14	12	6	5	4	4
	2	7	6	1	1	1	1
	3	2	2	0	0	0	0
Ocular							
Dry eye syndrome	1	6	5	6	5	4	4
	2	6	5	0	0	1	1
Syndromes							
Retinoic acid syndrome	1	1	1	1	1	0	0
	2	11	9	0	0	0	0
	3	9	7	0	0	0	0
	4	8	7	0	0	0	0

Adapted from Source Table 29 SR (grades with 0 patients, not included)

Myelotoxicity associated with ATO was also schedule dependent, because Grade 3-4 neutropenia occurred in 69 of 112 patients in CON1 compared with 30 of 112 patients in CON2. No Grade 3 to 4 thrombocytopenia was seen in either cycle of consolidation. QTc prolongation was less frequent during consolidation than during induction but the differences were not statistically significant. One episode of ventricular tachycardia occurred in a single patient during the first cycle of consolidation but this was transient

and was not associated with serious outcomes. Toxicities experienced by the 4 paediatric and adolescent patients (ages 3, 15, 16, and 17 years) were comparable with those seen in adult patients. During medical nutrition therapy (MNT) therapy AEs were more frequent and more severe during the earlier cycles of MNT. There were no cases of central nervous system (CNS) haemorrhage, 2 cases of gastrointestinal haemorrhage and 3 cases of pulmonary haemorrhage.

SAEs reported in the clinical studies included APLDS, ECG abnormalities, hyperleukocytosis, neutropenia and thrombocytopenia. Lo-Coco et al (2013) reported APLDS in 15 (19%) of the ATRA + ATO patients and 13 (16%) of the ATRA + CT patients. It was considered severe in 5 patients from each group, and fatal in 2 patients from the ATRA + CT group. Powell et al (2010) noted that APLDS occurred in 177 patients (37%; 177/481) during induction, while in Dai et al (2009) only 5 patients (of the 162 patients) were reported to have had APLDS (3 in the ATRA + ATO group and 2 in the ATRA group) and none of these patients died. Overall, no new or unexpected SAEs were reported in the clinical studies.

Clinical laboratory data was not reported in most of the RCTs. However, based on the known hepatotoxicity of ATO increases in LFTs were noted. In the study published by Shen et al (2004) a total of 29 patients reported liver dysfunction (Grade 1 to 4). Only four patients in the ATO group had Grade 3-4 toxicity. Following dose reduction of ATO (grade 1) and supportive therapy or cessation of ATO (higher grades) the liver function of 19 patients returned to normal within 1 week and the remaining 10 patients within 1 - 2 weeks. ATO was not required to be stopped completely in any of the patients in this study.

While ECG was used to monitor QT interval most of the RCTs did not report details of ECG or vital signs data. Arsenic levels were not measured in any of the combination studies.

The adverse effect profile for ATO includes some unique toxicity. ATO can cause differentiation syndrome similar to ATRA. The occurrence of differentiation syndrome is limited to the induction cycle. In the pivotal APDLS study, incidence was 14% during induction but no deaths were attributable to APDLS. Similar results were observed in the other clinical trials. Monitoring for unexplained fever, dyspnoea, weight gain, pulmonary infiltrates, pleural or pericardial effusions and leucocytosis during induction and management of differentiation syndrome by immediate initiation of high dose corticosteroids (for example, dexamethasone 10 mg IV twice daily), supportive care and temporary discontinuation of ATO were useful.

ATO also can cause QT interval prolongation. In the APML4 study, incidence of QT prolongation >500 ms was 14% but there were no instances of torsade de pointes or other serious arrhythmias. The prescribing information recommends that a 12-lead ECG be performed at baseline and weekly during induction and consolidation therapy. Levels of potassium, magnesium and calcium should be monitored and abnormalities should be corrected in patients receiving ATO therapy.

Other potential toxicities include liver function abnormalities, peripheral neuropathy, gastrointestinal effects, rash, hyperglycaemia and myelosuppression. Most toxicity can be managed with supportive care, ATO dose reduction, temporarily withholding ATO treatment or a combination of these options.

The findings from the pivotal combination therapy studies confirm the distinct side effect profiles of ATRA combined with ATO and ATRA combined with CT. The ATRA + CT combination results in more frequent prolongation of cytopenias, mucositis and infections, whereas the ATRA + ATO combination results 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; hydroxyurea was used to counteract hyperleukocytosis.

Safety of ATO as monotherapy in newly diagnosed APL

In the Ghavamzadeh studies (2006, 2011) involving up to 197 patients with newly diagnosed APL, ATO monotherapy was associated with 14% incidence of early death during induction phase and high incidence of hyperleukocytosis (58%) and hepatotoxicity (35%). In the Matthews studies (2006, 2010), APDLS occurred in only 5 (6.9%) patients which was lower than has been previously reported. The low incidence of cardiac-related toxic events in this series of newly diagnosed cases of APL could potentially be due to absence of exposure to anthracyclines or other cardiotoxic agents prior to this therapy and the attention to maintenance of electrolyte levels within the normal range. Furthermore, it is possible that transient QTc prolongations were missed due to lack of cardiac monitoring. Interpretation of this long term safety results was limited as details of methodology used to collect the follow-up data was not provided. There was a high incidence of hyperleukocytosis and hepatotoxicity in this small open label study evaluating single agent treatment with ATO in 17 newly diagnosed patients with APL (Alimoghaddam, 2006).

Safety results in the 2 paediatric studies (George, 2004 and Zhou, 2010) in 30 paediatric patients aged 4 to 15 years showed that treatment with ATO monotherapy in newly diagnosed APL showed similar adverse event profile to that observed in adults. However, number of patients and duration of follow-up was not adequate to assess long-term consequences in these patients.

The patients evaluated in the six ATO monotherapy studies were not representative of target patient population. ATO monotherapy is only indicated in newly diagnosed APL in patients in whom ATRA and/or CT is contraindicated. However, these patients were not specifically evaluated and in fact all patients in the ATO monotherapy studies were much younger (median age was 28 to 30years in 4 of these studies and 2 studies were in paediatric patients). Overall, the evidence for safety of ATO monotherapy in treatment of newly diagnosed APL was not adequate.

Overall safety conclusions

Arsenic trioxide has been available for some time now in the treatment of Relapsed and Refractory APL. The three most clinically important adverse events associated with the use of Arsenic trioxide are 'Differentiation Syndrome (APLDS)', cardiac arrhythmias associated with electrolyte imbalance and hepatotoxicity. These adverse events are all well recognised as the patients are treated in centres familiar with these issues and can be safely managed.

Arsenic retention is another major concern associated with use of ATO. Urine arsenic concentrations and arsenic contents in nails and hair, which are good indicators of long term exposure and in vivo accumulation of arsenic, were analysed in very few patients mainly in the paediatric single dose studies. Although the arsenic levels in urine, hair and nails from patients who had ceased treatment for less than 24 months were significantly greater than those in healthy controls, no significant difference was found between patients who had ceased treatment for more than 24 months and healthy controls. The urine arsenic concentrations in patients who had ceased treatment for more than 24 months were all below the safe limit of 200 μg/L set by the US Agency for Toxic Substances and Disease Registry (ARTSDR).

Overall, the AE profile of ATO combination therapy in newly diagnosed patients with APL was similar to the known AE profile of ATO in relapsed ATO and no new or unexpected AEs were identified. However, evidence for safety of ATO monotherapy in newly diagnosed APL in patients in whom ATRA and/or CT is contraindicated is not adequate.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Phenasen in the proposed usage are:

- Excellent response rates when used in combination with ATRA for newly diagnosed patients with APL. Results from the pivotal Phase II open label Study APML4 in 125 newly diagnosed APL patients demonstrate that induction and consolidation treatment with ATO with ATRA/CT results in CR of 95% at end of induction with median time to relapse of only 53 days and observed annual relapse-free rates of 97.3% at 1 and 2 years and 95.4% at 3, 4 and 5 years. Furthermore, use of ATO in the consolidation cycle enabled reduced exposure to CT as it substituted IDA (which was used in Study APML3).
- Rapid onset of CR following combination treatment with ATRA+ATO with median duration to CR ranging from 25 to 53 days in the 4 main combination studies.
- May be used instead of chemotherapy in adults with newly diagnosed APL especially in patients not likely to tolerate chemotherapy
- Some evidence of efficacy when used as single agent in newly diagnosed patients with APL although efficacy appears to more evident in patients with low/intermediate risk.
- Risks associated with ATO such APDLS and haemorrhagic complications can be managed by aggressive monitoring and supportive treatments including corticosteroids, hydroxyurea and platelet infusions.
- Limited risk of myelosuppression, although long term risks of ATO such as hepatotoxicity, prolonged QTc interval, secondary cancers and so on cannot be ruled out.

First round assessment of risks

The risks of Phenasen in the proposed usage are:

- APL differentiation syndrome.
- Hyper-leukocytosis,
- Hepatic toxicity
- Prolongation of QTc interval
- Chronic arsenic toxicity
- The risk of development of secondary cancers resulting from ATO exposure is not known.
- Greater risk of APDLS and early death was associated with high risk (especially WBC $>10x10^9$/L) compared to those with low/intermediate risk.
- The studies evaluating ATO monotherapy for newly diagnosed APL did not specifically evaluate target patients, that is, those in whom ATRA and/or chemotherapy was contraindicated. In fact majority of patients in the monotherapy studies were younger (median age 28 to 30 years) and 2 studies evaluated paediatric patients aged 4 to 15 years.

First round assessment of benefit-risk balance

The standard treatment for patients with newly diagnosed APL is the combination of ATRA and chemotherapy. Chemotherapy during induction and consolidation has typically consisted of an anthracycline, specifically daunorubicin or idarubicin with or without cytarabine. Some regimens have included a maintenance phase that consists of ATRA with oral methotrexate and mercaptopurine.

Prior to the introduction of ATRA, APL was among the most fatal subtypes of AML at presentation or during induction, primarily because of an associated complex and often catastrophic bleeding disorder. However, since the advent of ATRA in the late 1980s and arsenic trioxide (ATO) in the late 1990s, progress in the treatment of APL has changed its course from a highly fatal to a highly curable disease. Despite the dramatic improvement in the treatment outcome of APL, treatment failure still occurs due most often to early death. Relapse has become increasingly less frequent, most commonly occurring in patients with high risk disease. A major focus of research for the past decade has been to develop a risk adapted treatment strategy to reduce treatment related morbidity and mortality in low and intermediate risk or older patients while targeting more intensive or alternative therapy to those patients at most risk of relapse.

Early detection of relapse is now possible by monitoring of the molecular marker of the disease, the *PML-RARα* fusion transcripts. Minimising the toxicities of cytotoxic chemotherapy may further improve the outcome in APL, particularly for older adult patients who account for 15% to 20% of patients with APL. In general, the CR rate for patients older than 60 years is significantly lower than that of younger patients. This is typically due to a higher incidence of early death owing to infection and bleeding. The outcome for this population can be improved by taking advantage of high sensitivity of the disease to anthracyclines and omitting cytarabine.

One Phase II study (APML4) and other controlled and uncontrolled studies (publications only) were submitted to support use of ATO in combination with ATRA and CT in newly diagnosed previously untreated APL. All efficacy and safety assessments were considered standard, widely used and generally recognised as reliable, accurate and relevant.

The APML4 trial from the Australasian Leukaemia and Lymphoma Group evaluated the combination of ATO, ATRA and IDA for induction therapy in 124 patients with newly diagnosed, previously untreated APL. Consolidation consisted of two cycles of ATRA and ATO alone and maintenance consisted of 2 years of ATRA, methotrexate and mercaptopurine. The simultaneous administration of ATRA and anthracycline-based chemotherapy is currently considered the standard induction treatment in newly diagnosed patients with APL. With regards to the choice of anthracyclines, no prospective randomised trials have compared daunorubicin and idarubicin in APL. IDA was used in studies APML4 and Lo Coco, 2013, but DA was used in studies published by Dai (2009), Shen (2004) and Powell (2010).

In the APML4 study, the complete remission rate was 95%, DFS at 2 years was 97.5% and therapy was generally well tolerated. Additionally, the patients' exposure to an anthracycline was reduced while maintaining the positive outcomes expected in this population. The study by Lo-Coco et al, (2013) shows that a combination of ATRA and ATO given for induction and consolidation therapy is at least not inferior and is possibly superior to standard ATRA and anthracycline based CT for adults with newly diagnosed, low to intermediate risk APL. The observed advantage in the 2 year EFS (which was primary efficacy endpoint) with ATRA + ATO compared to ATRA +CT (97% versus 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-leukemic efficacy. The study reported CR in all (100%) ATRA+ATO patients after a median 32 days of induction. Dai et al (2009) reported high rates of RFS with combination treatment,

while patients receiving ATRA alone had significantly higher relapse rates and lower RFS. The estimated OS of 85% reported by Ravandi et al (2009; with a median 99 weeks follow up) is in line with the results from other studies.

The study reported by Powell et al (2010) involving 481 patients with newly diagnosed APL shows that addition of As_2O_3 to consolidation therapy to regimens using ATRA and anthracycline based CT improves EFS with similar results reported by Gore (2010). Overall, there was adequate evidence to support use of ATO in combination with ATRA and/ or CT in newly diagnosed, previously untreated patients with APL.

The proposed dosing regimen for ATO as combination therapy for newly diagnosed APL was used in the 3 pivotal studies (APML4 study, Lo Coco, 2013 and Dai, 2009). Results from the large study involving 481 newly diagnosed patients with APL (Powell, 2010) demonstrated that As_2O_3 given as initial consolidation therapy is safe and improves event-free, disease-free, and overall survival for newly diagnosed patients with APL. Similar results were observed in Gore et al 2010. However, both studies did not use As_2O_3 for remission induction.

As a single agent, ATO can induce CR in 85 to 86% of patients with untreated newly diagnosed APL, comparable with that achieved by ATRA-based therapy (Ghavamzadeh et al. 2006; Mathews et al. 2006). The most benefit from ATO monotherapy during induction and consolidation is observed in patients with the WBC counts of <5000/μL and platelet counts >20,000/μL at diagnosis with an EFS of 100% at 3 years. However, the outcome of patients with WBC >5000/μL at diagnosis appears to be inferior to a similar subset treated with ATRA plus chemotherapy, with an EFS of only 67% and a higher early death rate of 14.4% mostly from haemorrhagic complications (Mathews et al. 2006). Therefore, therapy with single agent ATO does not appear sufficient for many patients as a frontline therapy. Furthermore, due to risk of early mortality during remission induction phase with ATO treatment, it is important to determine the subgroups of patients likely to benefit from ATO monotherapy. The sponsors proposed that ATO be used as single agent therapy in newly diagnosed APL in patients in whom ATRA and/or chemotherapy is contraindicated. However, the patients evaluated in the six monotherapy studies did not represent this target patient population (2 of 6 studies included only paediatric patients aged 4 to 15 years and median age of patients in other studies was only 28 to 30 years). Patients with contraindications to ATRA and/or chemotherapy are more likely to be elderly patients with comorbidities but these patients were not evaluated in any of the submitted single agent ATO studies.

The AE profile observed in newly diagnosed patients with APL was similar to the known AE profile of ATO in relapsed ATO; that is, no new or unexpected AEs were identified. The common AEs (>1% incidence) reported in the RCTs is summarised in Table 11. The safety results reported in the RCTs confirmed the expected AE profile as patients receiving ATRA alone or ATRA + CT had more frequent prolonged cytopenias, mucositis and infections, while groups given ATRA + ATO had more frequent prolonged QTc and liver function abnormalities (Lo-Coco et al, 2013, Shen et al, 2004). The majority of AEs were managed with reduction of the dose of ATO, discontinuation of treatment or through supportive care. Arsenic levels in urine, hair and nails were only measured in the paediatric studies and did now show significant accumulation although long term follow-up was not available.

Table 11: Common AEs reported in RCTs (occurring in ≥1% of patients)

Study Identifier (Author)	Adverse Events	No. of Patients (%)		
		ATO	ATO + ATRA	ATRA or ATRA+CT
Lo-Coco et al[3] 2013, module 5.3.5.1.1	§ n=68 †n=69		*(n=77)*	*(n=79)*
	Haematologic:			
	Gr 3 or 4 neutropenia and/or		35 (46)	62 (79)
	Thrombocytopenia (>15 days),		45 (59)	70 (88)
	Hyperleukocytosis		35 (47)	19 (24)
	Non-haematologic:			
	Hepatic (Grade 3 or 4)		43 (63)§	4 (6)†
	Prolonged QTC interval		12 (16)	0
Shen et al[6], 2004 , module 5.3.5.1.2		*(n=20)*	*(n=20)*	*(n=21)*
	Haematologic:			
	Hyperleukocytosis	12 (67)	14 (70)	10 (53)
	Non-haematologic:			
	Hepatic (Grade 3 or 4)	2 (10)	2 (10)	1 (5)
	Dry mouth	2 (11)	12 (60)	11 (58)
	Headache	1(6)	2 (10)	4 (21)
Powell et al[5], 2010, module 5.3.5.1.3			*(n=244)*	*(n=237)*
	Haematologic			
	Grade 3		(21)	(16)
	Grade 4		(54)	(67)
	Non-haematologic			
	Grade 3		(41)	(30)
	Grade 4		(5)	(5)
	Headache (Grade 3)		(7)	(3)
	Nausea (Grade 3)		(4)	(3)
	Electrolyte abnormalities (Grade 3)		(3)	(1)
Dai et al[4], 2009 module 5.3.5.1.4			*(n=90)*	*(n=72)*
	Haematologic:			
	Hyperleukocytosis		'common'	'common'
	Non-haematologic:			
	Hepatotoxicity: Total		56 (62)	14 (19)
	Grade 1		33(37)	8(11)
	Grade 2		15 (17)	4(6)
	Grade 3		7(8)	2(3)
	Grade 4		1(1)	0
	Dry lips		41 (46)	30 (42)
	Headache		18 (20)	13 (18)
	Skin reaction		14 (16)	10 (14)
	Fluid retention		21 (23)	5 (7)
	Differentiation Syndrome		3 (3)	2(3)

Due to overall effectiveness of ATO and its ability to minimise administration of chemotherapy, ATO has a potential role in the treatment of newly diagnosed, previously untreated APL. However, ATO administration has its own administration and toxicity issues that must be considered (hepatotoxicity, prolonged QTc interval, APDLS and so on) although many of these can be managed with aggressive monitoring and supportive treatment or ATO dose reduction or temporary withdrawal.

The benefit-risk balance of Phenasen is unfavourable given the proposed usage but would become favourable if the changes recommended below (*First round recommendation regarding registration*) are adopted.

First round recommendation regarding authorisation

It is recommended that the submission be rejected for the proposed extended indication for Phenasen '*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 chemotherapy unless ATRA and/or chemotherapy is contraindicated.*'

Approval for a modified indication for use as combination therapy in previously untreated patients with APL may be granted subject to incorporation of changes suggested in First round comments and adequate response to questions to the Clinical questions.

However, the evidence to support efficacy/ safety of Phenasen as single agent in newly diagnosed, previously untreated patients with contraindications to ATRA and/or chemotherapy is not adequate.

Clinical questions

Efficacy

Question 1:

'*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 chemotherapy unless ATRA and/or chemotherapy is contraindicated.*'

The sponsors have not specified that arsenic trioxide be used as single agent in the wording of the indication although it is implied as suggested by the proposed PI 'Dosing and administration' section. It has not been specified if ATO could still be used with either ATRA or chemotherapy depending on which treatment was contraindicated. Could the sponsors please provide clarification on this issue?

Question 2

The proposed indication also implies that single agent treatment with ATO is to be used in patients with previously untreated APL if ATRA and/or chemotherapy is contraindicated. However, the published studies submitted to support this did not specifically evaluate this patient population. Two of the 6 ATO monotherapy studies were conducted in paediatric patients aged 4 to 15 years and the median age in the other studies was 28 to 30 years with very few patients over 50 year. Patients with contraindications to ATRA and chemotherapy are more likely to be elderly patients with comorbidities but these patients were not evaluated in any of the submitted single agent ATO studies. Furthermore, it appears that patients at low/intermediate risk showed better results compared to those with high risk and this was shown in both Ghavmazadeh 2011 and Matthews, 2006 reports. Due to risk of early mortality during remission induction phase with ATO treatment, it is important to determine the subgroups of patients likely to benefit from ATO monotherapy. Could the sponsors justify use of ATO as single agent in patients with newly diagnosed APL with contraindications to ATRA and/or chemotherapy?

Question 3:

The sponsor's clinical summary of efficacy states the following:

> *Induction Regimen. During induction Group 1 received ATRA 25 mg/m^2/day orally, Group 2 received ATO 0.16 mg/kg/day iv and Group 3 received both ATRA 25 mg/m^2/day orally and ATO 1.16 mg/kg/day iv concurrently.*

There seems to be a typo as the last line should read Group 3 received both ATRA 25 mg/m^2/day orally and ATO 0.16 mg/kg/day IV concurrently.

Question 4

One table in the sponsor's Clinical summary has errors in reporting results of the Lou et al, 2013 study. The results observed in the high risk and low/intermediate risk groups have been misrepresented. Could the sponsors provide clarification on this issue?

Second round evaluation of clinical data submitted in response to questions

There was no Second round clinical report conducted.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an Australian Risk Management Plan (AUS-RMP version 2 dated 15 October 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 12.

Table 12: Summary of Ongoing safety concerns

Important identified risks	APL Differentiation syndrome ECG abnormalities Peripheral neuropathy Hyperleukocytosis Neutropenia Thrombocytopenia Prolongation of QTc interval Hepatotoxicity
Important potential risks	Hypersensitivity to arsenic
Important missing information	Patients under 5 years of age, elderly patients, pregnant or lactating women, patients with hepatic or renal impairment, patients of different ethnic origin (data on Chinese and Australians only) Effect of medication errors and overdoses

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance to monitor all the safety concerns.

The following statements have been provided in regard to the need for additional pharmacovigilance:

'*At the present time, given the following key points:*

- *The well-defined safety profile for arsenic trioxide in the clinical setting;*
- *The apparent safety of the current formulation when administered in the clinical trial and post-marketing settings;*
- *The intended usage for the product - in a hospital environment where patient's clinical status is intensely monitored.*

Phebra does not feel that the implementation of additional pharmacovigilance activities is warranted at this time. As indicated above, Phebra commits to continuing to monitor the risk/benefit ratio for this product and updating the planned pharmacovigilance activities, RMP, PI and all relevant documentation should it become evident that the risk/benefit balance requires significant amendment.'

Risk minimisation activities

The sponsor states:

'*The proposed risk minimisation activities consist of routine risk minimisation (e.g. measures associated with the labelling, the package leaflet (approved product information), the pack size and the legal status of the product. Phenasen® is available only to medicinal prescription. It should be noted that this product is intended for use by highly trained medical professionals within the hospital setting, as a consequence of this, the patient population in which this will be administered will be more closely monitored. It is proposed that this will result in any adverse events relating to the use of Phenasen® being more easily identified, reported and dealt with. This reduces the risks associated with its use or misuse.*'

Reconciliation of issues outlined in the RMP report

Table 13 summarises the First round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.'

Table 13: Reconciliation of issues outlined in the First round RMP evaluation report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the clinical evaluators through the TGA's consolidated request for further information and/or the clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	Safety considerations were not raised by the clinical evaluators through the consolidated request and/or the clinical evaluation reports respectively.	The sponsor's response is satisfactory.
2. The version number and the date of the AUS-RMP are both provided as part of the document name of the RMP. In the next update, the sponsor should add a cover page for the RMP. The cover page should contain information including date of the document, version number, and data lock point.	The sponsor has included a cover page per suggested by the RMP evaluator for the revised RMP.	The evaluator has noted the addition of the cover page in the updated AUS-RMP. The sponsor's response is satisfactory.
3. Sudden death has been reported with patients treated with arsenic trioxide. Although no clear causal	The sponsor has included 'sudden death' as a potential risk per recommendation of the RMP evaluator in the revised RMP	The evaluator has noted the change to the updated AUS-RMP. The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
relationship has been established, 'sudden death' should be added as a potential risk.	version 3.	
4. The following adverse reactions are potentially serious and have been reported with the use of arsenic trioxide, these should be added as identified risks to the RMP: Dyspnoea (common); Seizures (common); Metabolic dysfunction including: hypokalaemia and hyperglycaemia (common); and hypermangnesaemia, hypernatraemia, ketoacidosis (uncommon); Arrhythmia including non-sustained ventricular tachycardia and premature ventricular contractions (very common); Cerebral vascular accident (uncommon); Pericardial effusion (uncommon); Haematological disorders including leucocytosis, haemorrhage, thrombosis (common).	The sponsor has included all the above mentioned adverse reactions (except for hypermangnesaemia) that are potentially serious and have been reported with the use of arsenic trioxide as identified risks to the RMP: The sponsor understands 'hypermangnesaemia' is a typographical error in the RMP evaluation report and it should be 'hypermagnesaemia'. Please note that 'hypermagnesaemia' is included as identified risks to the RMP.	The evaluator has noted the spelling mistake in the first round RMP evaluation report. The evaluator has noted that all the safety concerns have been added to the updated AUS-RMP as 'important identified risks'. The sponsor's response is satisfactory.
5. The sponsor states: '*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).*' Carcinogenicity should be added as a potential risk.	The sponsor has included carcinogenicity as potential risks to the RMP.	The evaluator has noted the change to the updated AUS-RMP. The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
6. The sponsor has provided search results regarding off-label use of arsenic trioxide. A few published research papers reported use of arsenic trioxide for different types of leukaemia, multiple myeloma, aplastic anaemia and other cancers. 'Off-label use' should be added as missing information.	The sponsor has included 'Off-label use' as missing information in the RMP.	The evaluator has noted the change to the updated AUS-RMP. The sponsor's response is satisfactory.
7. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as follows: Warning about pregnancy: arsenic trioxide is a category X drug. The approved EU Summary of Product Characteristics (SmPC) for the innovator product contains the following waring: *'Men and women of childbearing potential must use effective contraception during treatment with TRISENOX.'* In comparison, the Australian PI advises: '*PHENANSEN should not be given to patients who are pregnant.'* It is recommended that the same warning be added to the Australian PI to ensure safe use of the product. In addition, the advice for pregnancy test prior to the treatment should be considered. Treatment of overdose: the approved SmPC for the innovator product contains detailed instructions on the treatment of drug overdose as follows: *'If symptoms suggestive of serious acute arsenic toxicity*	**7a.** The sponsor has amended the product information to read as *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.* *PHENANSEN should not be given to patients who are pregnant. Pregnancy test prior to the treatment with PHENANSEN 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.* This information is included in the revised RMP document. 7b. Delegate has not	The evaluator has noted the sponsor's response. The recommendations regarding the PI remain for the Delegate's consideration.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
(e.g. convulsions, muscle weakness and confusion) appear, TRISENOX must be immediately discontinued and chelating therapy with penicillamine at a daily dose ≤ 1 gm 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 medication, 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 ≤ 1 gm 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.' The approved product labelling in the USA for the innovator products contains the following instructions on overdose: *'If symptoms suggestive of serious acute arsenic toxicity (e.g., convulsions, muscle weakness and confusion) appear, TRISENOX (arsenic trioxide) injection should be immediately discontinued and chelation therapy should be considered. A conventional protocol for acute arsenic intoxication includes dimercaprol administered at a dose of 3 mg/kg intramuscularly every 4 hours until immediate life-*	recommended for any modification in this section. Currently our PI has the following information on 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.* Symptoms of overdose with the arsenic trioxide are similar to reported side effects of this medication. Management of these side effects are clearly mentioned in the Product Information. Hence, the sponsor feels that the given information is adequate and propose not to amend the overdosage section. 7c. Delegate has not recommended for any modification in maximal treatment duration in patients refractory to, or relapsed from retinoid and anthracycline therapy. The TOXNET information for arsenic trioxide recommends ATO use until bone marrow remission and not to exceed 60 doses. The sponsor feels that the given information is adequately justified and hence not proposing to amend this section.	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
threatening toxicity has subsided. Thereafter, penicillamine at a dose of 250 mg orally, up to a maximum frequency of four times per day (≤ 1 g per day), may be given.' It is recommended that the Delegate considers the instruction provided in the Australian PI in the context of the local practice. Maximal treatment duration in patients refractory to, or relapsed from retinoid and anthracycline therapy: there appears to be discrepancy between the approved SmPC for the innovator product and the proposed Australian PI. The Australian PI advises that dosing of arsenic trioxide must be discontinued if bone marrow remission has not occurred by day 60, whilst the SmPC allows only 50 days treatment. It is recommended that the Delegate considers the discrepancy in the context of clinical evidence.		
8. Where necessary, relevant parts of the CMI should be updated accordingly.	The sponsor has amended the consumer medicine information as per the recommendation of the Delegate. In the proposed CMI, the indication/usage of Phenasen is amended to read as Phenasen is used to treat acute promyelocytic leukaemia also known as APL, when other treatments have failed or the patient has relapsed. In newly diagnosed or previously untreated APL patients, Phenasen is used only in combination with all-trans retinoic acid (ATRA) and/or chemotherapy. Annotated and clean copies of the revised Consumer Medicine Information (CMI) were	The evaluator has noted the changes made to the updated CMI. The following advice has been added: *'Men and women of childbearing age should use some kind of birth control while they are being treated with Phenasen. Your doctor will discuss this with you... Pregnancy tests may be done in women of childbearing age prior to the treatment with Phenasen… Men and women of childbearing age should take some kind of birth control precautionary method while they are being treated*

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	provided. The sponsor has also amended the CMI as per the RMP evaluator's recommendation and revised to include the warning and precaution about pregnancy and breast feeding. In addition, the advice for pregnancy test prior to the treatment and using precautionary contraceptive methods while on treatment with Phenasen are also included in the relevant sections of the CMI. Regarding treatment for overdose and duration of treatment in patients refractory to, or relapsed from retinoid and anthracycline therapy, the sponsor feels that the information currently available in the CMI is adequate. Hence the sponsor is not proposing to amend the overdosage section.	*with Phenasen.'* It is recommended to the Delegate that the wording be changed to: *'Men and women of childbearing age must use effective birth control while they are being treated with Phenasen. Your doctor will discuss this with you… Pregnancy tests should be done in women of childbearing age prior to the treatment with Phenasen…Men and women of childbearing age should take effective birth control precautionary method while they are being treated with Phenasen.'* As detailed advice on treatment for overdosage is a matter for clinicians, the current content of the CMI is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are summarised below**.**

Outstanding issues

Issues in relation to the RMP

Recommendation 7: The recommendation(s) on the draft Product Information remain and are for consideration by the Delegate.

Recommendation 8: The evaluator has noted the changes made to the updated Consumer Medicine Information (CMI).

The following advice has been added:

> *Men and women of childbearing age should use some kind of birth control while they are being treated with Phenasen. Your doctor will discuss this with you... Pregnancy tests may be done in women of childbearing age prior to the treatment with Phenasen… Men and women of childbearing age should take some kind of birth control precautionary method while they are being treated with Phenasen.*

It is recommended to the Delegate that the wording be changed to:

> *Men and women of childbearing age must use effective birth control while they are being treated with Phenasen. Your doctor will discuss this with you… Pregnancy tests should be done in women of childbearing age prior to the treatment with*

Phenasen…Men and women of childbearing age should take effective birth control precautionary method while they are being treated with Phenasen.

As detailed advice on treatment for overdosage is a matter for clinicians, the current content of the CMI is acceptable in the context of RMP.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

1. Implement AUS-RMP version 3 dated 20 April 2015 (data lock point 6 May 2012) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluation report considered the information supporting the application. No second round CER report was written. The sponsor's responses to the first round Clinical questions have been considered in this Delegate's Overview. A key change during the evaluation phase was the sponsor's modification of the proposed extension of indication to exclude the single agent use of ATO in newly diagnosed APL.

Overview of data

This was a hybrid submission, comprising:

- Study APML4, in Clinical Study Report format
- Relevant published papers obtained via systematic literature search (date of last search, 2 to 4 June 2014)

The sponsor's search strategy was endorsed by the TGA.

A summary of the literature presented in support of the application is given in Attachment 2. Studies considered pivotal in the CER were APML4, Lo-Coco et al (2013) and Dai et al (2009).

Pharmacokinetics (PK)

No new PK data were submitted.

Pharmacodynamics (PD)

No new PD data were submitted.

Efficacy

For context, the proposed main approach to use of ATO in newly diagnosed APL is:

- In *induction*, ATO (Days 9-36) in combination with ATRA *and* idarubicin.
- In *consolidation*, ATO in combination with ATRA (that is, no further anthracycline so that the total anthracycline exposure is relatively low, at 48 mg/m^2 idarubicin). The first cycle, CON1, is continuous; the second cycle (CON2) is intermittent.
- In *maintenance*, no proposed use of ATO.

Evidence in support of ATO's efficacy in newly diagnosed APL is summarised in the CER (Attachment 2). The studies were presented in the submission according to whether:

- ATO was being used in *combination* with other agents, or as a *single agent*; and
- the studies were *controlled* or *uncontrolled*

There was wide variation in sample size across presented studies.

There were several studies in exclusively in children with newly diagnosed APL, but these studies were of single agent ATO.

There was wide variation in details of treatment regimen, within each treatment phase (induction, consolidation, maintenance), across presented studies.

There was often a distinction made in the literature between high risk patients and others, typically on the basis of white blood cell count at baseline (≥ 10 x 10^9/L).[18]

The Delegate considers that APML4 provides the pivotal efficacy data in support of this application, mainly because *only* this study examined the particular approach to treatment of newly diagnosed APL that is proposed by the sponsor (use of ATO *and ATRA and* idarubicin in induction; use of ATO *and* ATRA in consolidation). However, the study did not include a control arm and the sponsor relies on historical comparison with Study APML3.

Study APML4 was conducted from 2011 to 2012 in Australia. It enrolled n=129 newly diagnosed APL patients (124 were evaluable). Patients were treated with the regimen under discussion in the application, along with obligatory prednisone and aggressive haemostatic support. Median age was 44 years (only 4 out of 129 patients were children). Some 19% had high Sanz risk; 54% had intermediate risk. Some 112 out of 124 (90.3%) completed induction and a further 4 out of 124 did not complete induction but attain complete remission. All 112 patients who completed induction achieved molecular CR by the end of CON2. Some 88% of these 112 patients completed all 8 maintenance cycles. Therefore, this study indicates that the sponsor's proposed approach to treatment of newly diagnosed APL is relatively successful. Further information about the study is presented in the CER (Attachment 2).

[18] '*Patients with APL may be stratified into three risk categories on the basis of white blood cell (WBC) count and platelet count. Low risk is a WBC count < 10x10^9/L and a platelet count > 40x10^9/L; intermediate risk is a WBC count < 10x10^9/L and a platelet count < 40x10^9/L; high risk is a WBC count > 10x10^9/L.*'

Other studies presented in the sponsor's submission do not directly support the use of ATO detailed in the sponsor's application.

Safety

Characterisation of ATO's safety in this setting is limited by the often brief description of safety methodology and outcomes in journal articles.

Study APML4's Clinical Study Report allowed more detailed characterisation of safety.

A total of 1214 patients were exposed to ATO as part of their study regimen, across submitted studies.

The ATO dose proposed for use, 0.15 mg/kg/day, is the same as that approved for second line use in APL. Duration of use is similar (for example, maximum exposure in the proposed first line approach is 81 days across IND, CON1 and CON2; the approved second line use allows for up to 85 days of dosing).

Safety in APML4 is particularly relevant because treatment regimens reflected regimens proposed for approval. Comparison with safety outcomes of APML3 is difficult, because these were not reported in detail. In APML4:

- During induction, Grade 3-4 APL differentiation syndrome was reported in 14% (ATRA + ATO), with no deaths. For sake of comparison, in APML3, 4 early deaths (4%) were ascribed to differentiation syndrome with the syndrome a 'major factor' in two of these four patients however the published paper did not detail frequency of Grade 3 to 4 APLDS. Also, corticosteroids were obligatory in APML4. The sponsor also notes that using clinical criteria (as opposed to CTCAE), only 8% had definite or severe ALPDS.
- During induction therapy, QTc prolongation to >500 ms occurred in 14% (there were no cases of Torsades de pointes or other severe arrhythmias). Transient ventricular tachycardia (VT) did occur in a patient during consolidation but QTc prolongation was less frequent than during induction.
- Biochemical hepatotoxicity was common but manageable. Iland et al (2014) noted '*an early attempt to establish a role for ATO in the initial therapy of APL stumbled when 7 cases of hepatic toxicity, including 2 fatalities, were observed among 11 patients*' but this experience appears unusual, based on the lack of fatal hepatotoxicity in data presented in this application.
- Neutropenia and febrile neutropenia were common SAEs.
- Consolidation treatment was associated with less toxicity than induction and CON2 was associated with less myelosuppression than CON1.

The safety outcomes of other studies are described on in the CER Attachment 2).

In the study by Lo-Coco et al (2013), while APLDS rates were similar across arms, onset of leucocytosis during induction was more common in the ATRA + ATO arm than the ATRA + CT arm (all cases were successfully managed with hydroxyurea). There was an impressive rate of hepatotoxicity in the ATRA + ATO arm (63% with Grade 3-4 hepatic toxic effects in induction or consolidation versus 6% in the ATRA + CT arm) but all cases resolved with temporary study drug discontinuation.

In single agent ATO studies, Ghavamzadeh et al (2006) reported APLDS; hepatic toxicity was not restricted to transaminitis, with hyperbilirubinaemia in 3 cases. Mathews et al (2006) reported APLDS in 6.9%; this occurred in patients with leucocytosis at baseline or in patients who developed leucocytosis with ATO treatment. Also, Mathews et al (2006) reported an association between homozygous mutant polymorphism of *MTHFR* 1298 (C/C) and hepatotoxicity (relative risk of 8.75), suggesting a role for MTHFR in the biotransformation of ATO.

The clinical evaluator noted that there are no adequate long-term safety data for use in children.

Clinical evaluator's recommendation

The clinical evaluator concluded that:

Approval for a modified indication for use as combination therapy in previously untreated patients with APL may be granted subject to incorporation of changes suggested in First round comments and adequate response to questions to the Clinical questions.

However, the evidence to support efficacy/ safety of Phenasen as single agent in newly diagnosed, previously untreated patients with contraindications to ATRA and/or chemotherapy is not adequate.'

Risk management plan

A risk management plan (AUS-RMP version 2 dated 15 October 2014) was submitted with this application. The RMP evaluator suggested some modifications to the RMP but there were no major objections to the nature of the RMP supplied by the sponsor. Only routine pharmacovigilance and risk minimisation activities have been proposed.

In APML4, there was considerable emphasis on risk mitigation, for example via obligatory use of prednisone, aggressive haematological support and so on. It will be necessary to encourage continued use of such risk mitigation, outside of the clinical trial context, to maintain the good outcomes seen in APML4. Documentation in the PI of approaches used in APML4 may help. Broadly acceptable text is already included in the Dosage and Administration section of the PI.

Risk-benefit analysis

Delegate's considerations

Efficacy endpoints

Iland et al (2014) describe relevant efficacy parameters in this setting:

> Several types of failure can occur during the treatment of patients with APL, and can broadly be categorised as:
>
> a. ED (early death), defined as death during, or as a consequence of, induction therapy;
> b. failure to achieve complete remission (CR) due to resistant disease;
> c. relapse (including both molecular and/or haematologic relapse); and
> d. death complicating post-remission therapy.

In submitted studies, early death was often due to CNS or pulmonary haemorrhage. APL induces a coagulopathy, and the CNS may be more susceptible to bleeding from this coagulopathy (Kwaan and Cull, 2014).

Since the proposed new usages of ATO are for induction of remission and consolidation, most emphasis is placed on endpoints that reflect efficacy of those phases of treatment. Long-term outcomes may be heavily influenced by initial treatment, but the assessment of long-term outcomes will presumably also be confounded by choice of maintenance. A caveat is that the proposed PI also recommends a particular maintenance strategy (that does not include ATO).

The proposed approach to induction, consolidation and maintenance

There is no 'global' consensus about the best approach to induction in newly diagnosed APL, as suggested by the tabulation in Sanz et al (2014) of recent schemes (Table 14). The tabulation does not attempt to factor in all approaches, for example the ATRA + ATO arm of the Lo-Coco et al (2013) study was not included.

The 'Australasian approach', consistent with the sponsor's proposal in this application, is conspicuous for its use of ATRA *and* chemotherapy *and* ATO in induction. Of major groups captured by Sanz et al, only the Shanghai group share this approach and only in patients with white cell counts >10 x 10^9/L.

Table 14: Sanz et al (2014). Recent schemes adopted by major groups based on conventional all-trans retinoic acid plus chemotherapy as backbone treatment.

	Group (Ref.)	Induction therapy	Consolidation therapy (no. of cycles)	Type of chemotherapy
ATRA + CHT alone	French–Belgian–Swiss [17]	ATRA + CHT (Dauno + Ara-C)	CHT (2)	Dauno + Ara-C
	MRC [29]	ATRA + CHT (Idarubicin)	ATRA + CHT (3)	Ida/MTZ
	GIMEMA/EORTC [12]	ATRA + CHT (Idarubicin)	ATRA + CHT (3)	Ida/MTZ ± Ara-C
	PETHEMA/ HOVON [13]	ATRA + CHT (Idarubicin)	ATRA + CHT (3)	Ida/MTZ ± Ara-C
	JALSG [28]	ATRA + CHT (Idarubicin)	CHT (3)	Dauno/Ida/MTZ + Ara-C
ATRA + CHT with ATO	US Intergroup [11]	ATRA + CHT (Dauno + Ara-C)	ATO (2) → ATRA + CHT (2)	Dauno + Ara-C
	Shanghai [16]	ATRA + ATO (±CHT[a])	CHT (3)	Dauno/Homo + Ara-C
	Australasian [19]	ATRA + CHT → ATO (Idarubicin)	ATO + ATRA (2)	–
	North American[b], [18]	ATRA + CHT	ATRA + CHT (1) → ATO (1)	Dauno + Ara-C

CHT = chemotherapy; ATRA = all-*trans* retinoic acid; ATO = arsenic trioxide; Dauno = daunorubicin, Homo = homoharringtonine; Ida = idarubicin; MTZ = mitoxantrone.

[a] Patients who presented with WBC counts higher than 10 × 10^9/L before or during the ATRA/ATO treatment also received additional chemotherapy.

[b] Several North American institutions.

One view is that use of ATRA + chemotherapy is standard practice in this setting (Sanz et al, 2014), and that rigorous demonstration of ATO's role as proposed by the sponsor would be via randomised comparison of this backbone with or without ATO. Sanz et al (2014) note '*the real importance of this drug (ATO) in newly diagnosed patients is still being evaluated'*. The authors clearly distinguish between approaches that (a) use ATO to replace chemotherapy, and (b) use ATO to reinforce the ATRA + chemo backbone. In Lo-Coco et al (2013), the former approach was taken (in the 'experimental' ATO arm); in APML4, the latter approach was taken (in induction).

The Australasian group is also notable for setting aside chemotherapy in consolidation; other groups described by Sanz et al use 1-3 cycles of chemotherapy (alone, alongside ATRA or sometimes alongside ATRA and ATO) for consolidation. Lo-Coco et al (2013) is an endorsement of ATRA + ATO in consolidation, relative to ATRA + chemo.

There is also lack of consensus about appropriate chemotherapy (type of anthracycline; and role of cytarabine in high risk disease, as discussed by Iland et al, 2014).

The lack of consensus extends to maintenance therapy, which is relevant because the sponsor recommends a specific approach to maintenance in the PI (although ATO is not a maintenance agent). Sanz et al (2014), for example, state that '*the data available on the benefit of maintenance therapy in the context of state-of-the-art strategies do not allow (unequivocal) positioning, and it should probably be assessed taking into account the curative potential of the prior induction and consolidation therapy*'.

Regarding the 'lack of consensus' about details of use, it is notable that many aspects of the treatment of relapsed or refractory APL lack consensus (Iland et al, 2014), extending to such basic features as the dose of ATO that provides the best benefit versus risk balance.

Protocols that minimise exposure to anthracyclines are valuable if they retain efficacy, since excessive myelosuppression, cardiotoxicity and therapy-related myelodysplasia or AML are risks with anthracycline use.

Evidence to support the proposed approach

Sanz et al (2014) note a '*virtual absence of resistance after any combination of ATRA and chemotherapy for induction*' which reinforces the need for evidence to support the benefit of additional ATO in induction, for newly diagnosed patients.

Evidence in support of use of ATO in newly diagnosed APL is from a variety of studies, all but one (APML4) in the form of published papers.

There is no common approach to the use of ATO across these studies, in that details of the timing of ATO, or the choice of concomitant agents, vary considerably. These details may influence the benefits and risks of the ATO 'approach' proposed by the sponsor. Only the APML4 study provides evidence in support of the key features of the sponsor's proposal, namely, use of ATO *and* ATRA *and* idarubicin in induction AND use of ATO *and* ATRA *without* chemo in consolidation. APML4 also supports the proposed maintenance regimen (though this does not include ATO).

Published studies are generally supportive of the efficacy of ATO, rather than supportive of the detailed regimen proposed by the sponsor. While APML4 was supportive of the specific regimen proposed and was a well-conducted study, it did not include a control arm. Comparison with APML3 is beset by typical problems attached to use of historical controls, as detailed in the TGA adopted guideline Note for Guidance on Choice of Control Groups in Clinical Trials[19].

While APML4 is influential in suggesting that addition of ATO to induction regimens and use of ATRA+ATO in consolidation can reduce exposure to anthracyclines without compromising cure rates, a concern is whether these results have been reproduced by other groups.

Impact on efficacy of ATO as a second-line agent

No data inform about whether use of ATO in first line will impact on the efficacy of ATO in relapsed/refractory patients. In this regard, the formal second line indication for ATO is for use in patients who are refractory to or have relapsed after use of retinoid (ATRA) and anthracycline chemotherapy. If ATO becomes part of initial therapy, its role in second line therapy becomes less clear. There are a few papers that describe resistance to ATO (Zhu et al, 2014; Lehmann-Che et al, 2014). The sponsor is invited to comment.

High risk disease

The clinical evaluator argued that:

> *'efficacy and safety has been shown predominantly in newly-diagnosed patients with low-to-intermediate risk APL' and that this should be specified in the PI, 'especially in light of the fact that patients with more severe newly diagnosed APL may benefit from more intensive chemotherapy'.*

In the sponsor's response, Phebra chooses not to specify use only in low-to-intermediate risk APL. Some studies suggested worse outcomes in high risk subjects than in others (for example, Lou et al, 2013) but this is to be expected. There is no particular signal of net harm via ATO in this risk group and the evidence base for use of ATO in high risk patients is similar to the evidence base in other patients. An exception is that Lo-Coco et al (2013) did not study high risk patients. The paper's authors state in this regard:

[19]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf>; see sections 1.3.5 and 2.5

> *The decision to exclude patients with high-risk disease was based on three main factors: the results of arsenic trioxide treatment with or without ATRA in these patients were reported to be significantly inferior to the results in low-to-intermediate-risk patients[22-25]; prolonged event-free and overall survival was routinely achieved in high-risk patients with risk-adapted consolidation therapy that included cytarabine[7,8,38] and there was concern about a potential increase in cases of the differentiation syndrome.*

References 22-25 are Ghavamzadeh et al (2011); Estey et al (2006)[20]; and Mathews et al (2006). Ghavamzadeh et al (2011) and Mathews et al (2006) were uncontrolled studies that considered single agent ATO. The Estey et al (2006) study employed gemtuzumab ozogamycin in high risk subjects; it was also uncontrolled. There is recent experience from APML4 that suggests the early death rate is not worryingly high or suggestive of a drug effect. In APML4 a reasonable proportion of patients (23 out of 123 with data, or 19%, by Sanz criteria; identical frequency according to WBC >10 x 10^9/mL) was high risk and there was no association with time to relapse from end of consolidation. The Delegate considers the sponsor's position is reasonable.

Interestingly, National Comprehensive Cancer Network (NCCN) Guideline[21] Version 1.2015 supports use of the APML4 protocol *only* in high risk patients (and then, only in those able to tolerate anthracyclines). However, ATO is also endorsed there in other newly diagnosed patients, with an algorithm as per Lo-Coco et al, 2013.

Low to intermediate risk disease

The Lo-Coco et al (2013) trial showed superiority of ATRA + ATO over ATRA + chemo in low-intermediate risk disease, and results in the ATRA + ATO arm were impressive. It is problematic to compare the low-intermediate risk subgroups of APML4 with the ATRA + ATO arm of Lo-Coco et al (2013). One conclusion is that both approaches appear to be successful in patients with low to intermediate risk disease. The PI for Phenasen should acknowledge that other approaches to treatment of newly diagnosed APL have met with good success, for example as per Lo-Coco et al (2013) in low-intermediate risk patients.

Safety

The safety of the proposed use of ATO in newly diagnosed APL does not appear to be a major departure from safety in second line use, though there is the potential for synergism with the toxicity of other treatments (such as cardiotoxicity of idarubicin and hepatotoxicity of ATRA).

Use in children

APL makes up approximately 10% of childhood AML.[22] A focus of APL management in children is the cardiotoxicity of anthracycline therapy.

As noted in the CER (Attachment 2), many trials included adolescents and three (APML4; Ghavamzadeh et al (2006); and Mathews et al (2006)) included some younger children. Two papers described use of ATO as a single agent in children (George et al, 2004) or in adolescents (Zhou et al, 2010).

The proposed PI does not alter the existing statement that 'safety and effectiveness in paediatric patients below the age of 5 years have not been studied'.

[20] Ravandi et al (2009) reported long-term results from patients in the 2006 paper by Estey et al
[21] http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
[22] Kutny MA et al (2014). Treatment of paediatric APL: How does the therapeutic approach differ from adults? Best Practice & Research Clinical Haematology 27: 69–78

While approval of the proposed indication in newly diagnosed APL will endorse the use of ATO + ATRA + idarubicin in children (at least above 5 years of age), the recommended regimen does aim to minimise cumulative anthracycline exposure. This may not go far enough to prevent cardiotoxicity in children. (See comments about low to intermediate risk patients above.)

The proposed PI recommends the ATRA dose (45 mg/m^2/day orally in divided doses; for example, for up to 36 days in induction, for newly diagnosed subjects). Sanz et al (2014) refer to a lower dose of ATRA in children. The Vesanoid PI recommends in children a dose reduction if severe toxicity occurs, for example intractable headache (presumably via the dose dependent association between ATRA and pseudotumour cerebri). Therefore, the text in the current PI may be reasonable in this regard.

Situations where ATRA or idarubicin are contra-indicated

The sponsor initially requested an indication that allowed for monotherapy use (where ATRA 'and/or' chemotherapy were contraindicated). The indication was modified in response to the First round clinical evaluation report. Currently, the proposed indication allows for use of ATO in combination with ATRA and/or chemotherapy but not ATO alone.

ATRA is contraindicated as follows:

Tretinoin is highly teratogenic; it is strictly contraindicated in pregnancy. VESANOID must not be used by women of child-bearing potential unless effective contraception is practiced for at least one month before beginning therapy, during therapy and at least one month following discontinuation of therapy. Breast-feeding should be discontinued if therapy with VESANOID is initiated.

VESANOID is contraindicated for use in patients with known hypersensitivity to VESANOID or any of its components.

The use of VESANOID in combination with Vitamin A is contraindicated (see PRECAUTIONS Interactions with Other Medicines).

Idarubicin (Ebewe) is contraindicated as follows:

> *Idarubicin Ebewe is contraindicated in patients with severe renal and liver impairment or patients with uncontrolled infections. It should also not be administered to individuals with hypersensitivity to idarubicin or any other component of the product (see DESCRIPTION) and/or other anthracyclines.*
>
> *Idarubicin therapy is contraindicated in patients with severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias, persistent myelosuppression, or previous treatment with maximum cumulative doses of idarubicin and/or other anthracyclines and anthracenediones.*
>
> *Idarubicin Ebewe is contraindicated in pregnant women or women wishing to become pregnant (see Use in Pregnancy under PRECAUTIONS).*

There is also a statement that it should not be given to patients with pre-existing bone marrow depression induced by previous medicine or radiotherapy unless the benefit warrants the risk.

Accordingly, pregnant women should receive neither ATRA nor idarubicin. However, Phenasen is also Pregnancy Category X[23].

In patients with severe renal or liver disease, or some heart conditions, it is possible that ATO would be used with ATRA but not idarubicin. There is some evidence (such as Lo-Coco et al, 2013, in low-intermediate risk subjects) to support this general approach for

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

induction. The wording of the currently proposed PI allows for this possibility. On the other hand, the Phenasen PI states (in the Precaution about ECG abnormalities) that in patients with congestive heart failure, arsenic trioxide should not be given, except when the benefits 'outweigh' the risks.

Overall risk-benefit

Clinical benefit of the sponsor's approach to treatment of newly diagnosed APL must be considered in the absence of randomised studies against established comparators. This was the case in the initial registration of Phenasen in second line treatment of APL.

In the Delegate's view, the approach used in APML4 as adopted by the sponsor, is a good approach to treatment of newly diagnosed APL but there may be others. The APML4 proposed approach appears fairly distinct from various strategies used by major groups overseas. On the other hand, based solely on cross-study comparison, it appears to be efficacious and reasonably safe. While cross-study comparison is not ideal, it may be unrealistic to 'wait' for randomised data that answers every key question in this setting. The Delegate supports the approval of the current application, subject to provision of an acceptable PI.

An alternative wording of the indication might be constructed, separating induction and consolidation phases (for example, 'in combination with ATRA and idarubicin' for induction; 'in combination with ATRA' for consolidation). An advantage of the sponsor's proposal, as it stands, is that it technically allows for cases where, for example, idarubicin should not be used. The PI does not expand on these less typical circumstances, for example, in the 'Dosage and Administration' section. This is acceptable, since treatment of newly diagnosed APL will be by highly specialised physicians.

Summary of issues

Evidence presented in support of the extension of indication was mostly in the form of published papers (sourced from a systematic search of literature up to 2 to 4 June 2014), hence a 'literature-based' submission.

One recent Australian study, APML4, was in the form of a Clinical Study Report. It included adequate information about study design, conduct and outcomes.

Only the APML4 study provided evidence of the efficacy and safety of the specific approach to treatment of newly diagnosed APL patients that the sponsor proposes. However, APML4 was an uncontrolled Phase II study. The sponsor's comparisons with Study APML3 introduce considerable risk of bias. On the other hand, APL is a relatively uncommon condition and it may be unreasonable to expect the sponsor to conduct randomised, controlled trials to show acceptable outcomes compared to the current standard of care, especially since there seems to be little consensus about the standard of care across induction, consolidation and maintenance phases of treatment that would be used in an acceptable control arm.

Other data, from published papers, are generally supportive of the role of ATO in newly diagnosed APL but do not provide direct support for the specific approach proposed in the PI.

The sponsor's proposed approach, as reflected in the 'Dosage and Administration' section of the proposed PI (see 'Dosage' above), is divergent from other general approaches to treatment of newly diagnosed APL, in that (a) there is a proposal to approve use of ATO *and* ATRA *and* idarubicin for induction of remission; (b) there is a proposal to remove chemotherapy from the consolidation phase of treatment.

This approach appears to be well supported by the results of APML4, but (a) good outcomes of APML4 are also in part due to intensive supportive care; (b) no other study provides an independent confirmation of the proposed approach.

At least one other approach, tested by Lo-Coco et al (2013), that is, the use of ATO + ATRA for both induction and consolidation, seems to produce very good outcomes (for low to intermediate risk patients). Technically, the proposed new indication 'allows' for this usage of ATO but the 'Dosage and Administration' section of the proposed PI does not countenance this approach. Latest NCCN guidance endorses APML4's approach *only* in high risk patients (and then, only if anthracyclines are tolerated). However, ATO is also endorsed in other newly diagnosed patients, with a different algorithm as per Lo-Coco et al, 2013.

Proposed action

The Delegate had no reason to say, at this time, that the application for the extension of indication of arsenic trioxide should not be approved.

Request for Advisory Committee on Prescription Medicines (ACPM) advice

1. Does the Phase II, uncontrolled study APML4 provide sufficient support for the detailed approach to treatment of newly diagnosed APL presented in the proposed PI?
2. Given the totality of data presented, is there a favourable benefit/risk balance for ATO in its proposed new usage?
3. Does the ACPM consider that the PI includes appropriate information about the proposed new usage?

Response from sponsor

Phenasen (arsenic trioxide or ATO) is a trivalent inorganic arsenical formulated as a sterile injectable solution. Phenasen is an antineoplastic agent (ATC code L01XX27: Antineoplastic and immune-modulating agents – Other antineoplastic agents).

The currently approved indication is:

> *'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.'*

The sponsor has proposed retaining the currently approved indication and including the additional indication:

> *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 current application proposing extension of the indication is a Mixed Type Application, that is, a combination of complete study reports of clinical studies carried out and supported with bibliographical references.

The submitted dossier included the Australasian Leukaemia and Lymphoma Group (ALLG) and Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) Phase II clinical trial (APML4) as the pivotal study. In 2003 the APML4 clinical trial sponsor, Australasian Lymphoma and Leukaemia Group (ALLG), requested from the sponsor a supply of Phenasen arsenic trioxide injection for a multi-centre clinical trial for

the treatment of APL (first line therapy). The APML4 study treated 124 de novo adult APL patients in a Phase II study with ATRA + ATO + idarubicin, induction with scheduling designed to minimise cardiotoxicity and the severity of APL differentiation syndrome.

The Gruppo Italiano Malattie Ematologiche dell'Adulto; German-Austrian Acute Myeloid Leukemia Study Group. *Retinoic acid and Arsenic trioxide for acute promyelocytic leukemia*[24] is one of the submitted published literature that supported the efficacy of arsenic trioxide in 162 low to intermediate risk *de Novo* APL patients. This was Lo-Coco *et al*, 2013, a prospective, randomised, open-label, Phase III, comparative, multi-centre, non-inferiority trial.

Sponsor's response on the Delegate's overview

Clinical efficacy

The sponsor is in agreement with the Delegate's following statements.

1. The 'Australasian approach', consistent with the sponsor's proposal in this application, is conspicuous for its use of ATRA and chemotherapy and arsenic trioxide in induction.
2. Lo-Coco et al (2013) is an endorsement of ATRA + ATO in consolidation, relative to ATRA + chemo.

The sponsor firmly believes that, the efficacy of Phenasen as proposed in the indication in high and low to intermediate risk APL patients is adequately justified.

High risk APL patients

The addition of arsenic trioxide in combination with ATRA and chemotherapy for induction for high risk newly diagnosed APL patients' is scientifically and ethically justified.

The beneficial effects are evident from the findings of APML 4 study. Evidence in support of use of arsenic trioxide in newly diagnosed APL is from a variety of studies in the form of published papers.

Until relatively recently, prior to the introduction of ATRA the outlook for patients with APL was dismal. There was a high mortality rate, particularly in the early phases of treatment and 5 year survival figures of 40% with chemotherapy were standard. The combination of medicines and chemotherapy improves the chances of survival in APL.

There is no particular signal of net harm via arsenic trioxide in the high risk group and the evidence base for use of ATO in high risk patients is similar to the evidence base in other patients.

The National Comprehensive Cancer Network (NCCN) has included arsenic trioxide in their guidelines for treating high risk APL patients (in those who are able to tolerate and also in those who are not able to tolerate anthracyclines) at induction and consolidation in combination regimens using ATRA with or without chemotherapy.

The sponsor does agree that APML 4 is a Phase II study in de novo APL patients. Considering the orphan status of the disease category APL, as suggested by the Delegate, it is unrealistic to 'wait' for randomised data that answers every key question in this setting. Updated results of APML4 study with median follow-up of 4.2 years were reported at the 2014 meeting of the American Society of Hematology, with 5 year OS and EFS rates of 94% and 90%, respectively, in all risk groups (87% and 83% in high-risk patients,

[24] N Eng J Med. 2013;369 (2):111-121

respectively). Tolerability and excellent long-term outcomes, the sponsor's approach for high-risk patients includes triple induction with ATRA, ATO and idarubicin.[25]

Low-to –intermediate risk APL patients

In low to intermediate risk newly diagnosed APL patients' the Lo-Coco trial showed superiority of ATRA + arsenic trioxide over ATRA + chemo arm and results in the ATRA + arsenic trioxide arm were statistically significant. The 2 year OS probability was 99% in the ATRA + arsenic trioxide group, as compared with 91% in the ATRA–chemotherapy group (P= 0.02). The 2 year DFS was 97% in the ATRA–ATO group and 90% in the ATRA–chemotherapy group (P = 0.11).

For patients with low-(to intermediate) risk APL, chemotherapy could safely be eliminated to reduce treatment associated toxicities and long-term complications observed with cytotoxic agents as therapy-related myeloid neoplasms have been observed in APL patients.

The standard of care for low risk patients no longer includes chemotherapy and the NCCN Guideline endorses the algorithm as per Lo-Coco et al, 2013.

Clinical safety

A total of 1214 patients were exposed to arsenic trioxide as part of their study regimen, across submitted studies. The sponsor is in agreement with the Delegate's following statements**.**

1. Study APML4's Clinical Study Report allowed more detailed characterisation of safety.
2. The safety of the proposed use of ATO in newly diagnosed APL does not appear to be a major departure from safety in second line use, though there is the potential for synergism with the toxicity of other treatments (such as cardiotoxicity of idarubicin and hepatotoxicity of ATRA).
3. There are no adequate long term safety data for use in children.

Sponsor's comment on ATO's role in second line therapy if ATO becomes part of therapy for de novo APL patients.

Arsenic trioxide with ATRA and/or chemotherapy is one of the treatment options for the newly diagnosed APL patients, recommended by the NCCN.

Other current treatment options for APL usually include an induction phase with all-trans retinoic acid (ATRA) and chemotherapy with idarubicin/cytarabine/daunorubicin/cladribine followed by a consolidation phase of chemotherapy and maintenance therapy with ATRA with or without low dose chemotherapy for 1 to 2 years. This treatment strategy results in a high complete remission 90% of the newly diagnosed APL patients after initial therapy and 80% of patients are cured of their disease.[26] However, about 5% to 30% of patients who have received this treatment relapse, mainly patients with high-risk APL.[27] Up to 30% of patients with APL who have achieved complete remission have experienced relapse. In

[25]Coombs CC, Tavakkoli M and Tallman MS (2015). Acute promyelocytic leukemia: where did we start, where are we now, and the future, Blood Cancer Journal 5, e304; doi:10.1038/bcj.2015.25; published online 17 April 2015

[26]Coombs CC, Tavakkoli M and Tallman MS, Acute promyelocytic leukemia: where did we start, where are we now, and the future, Blood Cancer Journal 5, e304;
doi:10.1038/bcj.2015.25; published online 17 April 2015

[27]Sanz MA, Montesinos P, Rayon C, Holowiecka A, de la Serna J, Milone G et al. Risk adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood 2010; 115: 5137–5146.

order to detect APL relapse the NCCN recommends Reverse transcription polymerase chain reaction (RT-PCR) testing after consolidation cycle.

Arsenic trioxide is currently regarded as the best treatment option in relapsed APL. The sponsor believes that, those who experience relapse or who are refractory to ATRA and chemotherapy and not exposed to arsenic trioxide would still benefit from Phenasen as second line therapy. Considering the fact that APL is already an orphan indication in Australia and ethical reasons, the sponsor believes the second line therapy Phenasen is important and should be available for this small population of patients.

4.1.4 Overall risk benefit analysis

The Delegate has reported that '*the clinical benefit of the sponsor's approach to treatment of newly diagnosed APL must be considered in the absence of randomised studies against established comparators… While cross-study comparison is not ideal, it may be unrealistic to 'wait' for randomised data that answers every key question in this setting. The Delegate supports the approval of the current application, subject to provision of an acceptable PI.*'

The sponsor is retaining the proposed indication as it is clear and concise. The proposed indication technically allows for cases where, for example, idarubicin should not be used. Hence, the sponsor believes that no alternative wording is required as suggested by the Delegate.

Conclusion

Phebra is in agreement with the Delegate's assessment of the application and clinical evaluation report.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Phenasen concentrated injection, containing 10 mg / 10 mL of arsenic trioxide to have an overall positive benefit–risk profile for the indication;

> *Phenasen is indicated 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.*

In making this recommendation the ACPM;

· noted that the data presented demonstrated efficacy in APL with manageable toxicity.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the Phase II, uncontrolled study APML4 provide sufficient support for the detailed approach to treatment of newly diagnosed APL presented in the proposed PI?

The ACPM advised that although study APML4 was not randomised, the results supported treatment of newly diagnosed APL with arsenic in combination with ATRA and/or chemotherapy.

2. Given the totality of data presented, is there a favourable benefit-risk balance for ATO in its proposed new usage?

The ACPM noted the increased survival rate was partly due to a decrease in the death rate by eliminating the use of unnecessary and toxic drugs rather than due to better supportive care, combined with increased efficacy when arsenic is used as first-line therapy in combination with ATRA and/or chemotherapy. The ACPM advised that the toxicity of using arsenic in this setting was manageable using current standard of care.

3. Does the ACPM consider that the PI includes appropriate information about the proposed new usage?

The ACPM noted that the indication only included APL characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression. The ACPM noted that other variations of APL are treated with the same therapy. The ACPM queried whether the indication could omit specifying any characterisation of APL and whether the sponsor had data to support broadening of the indication.

4. With regard to use in paediatric APL, are there any particular issues with regard to approval of the application and/or the PI?

The ACPM acknowledged that there are insufficient paediatric patients with APL to enrol in a randomised study. However, the ACPM considered the data were sufficient to support use of arsenic as first-line therapy for paediatric patients.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Phenasen (arsenic Trioxide Injection 10 mg/10 mL) is presented in 10 mL vials in cartons of 10 for intravenous infusion, indicated for:

> *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*

Specific conditions of registration applying to these goods

The arsenic trioxide AUS-RMP version 3 dated 20 April 2015 (data lock point 6 May 2012) and any future updates as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Phenasen at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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