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Committee for Medicinal Products for Human Use (CHMP)

Trisenox

arsenous acid anhydride

Procedure No. EMEA/H/C/388/Article 45 044

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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INTRODUCTION

Trisenox (arsenic trioxide or ATO) is a trivalent inorganic arsenical formulated as a sterile injectable solution, approved for the following therapeutic indication: « Induction of remission and consolidation in adult patients with relapsed/refractory acute promyelocytic leukaemia (APL), characterised by the presence of the t(15 ;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy ».

Trisenox is administered as an intravenous infusion for induction treatment at a fixed dose of 0.15 mg/kg/day given daily until the bone marrow remission is achieved without overage 50 doses. Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy at the rate of 0.15 mg/kg/day for 25 doses given over 5 weeks (5 days per a week).

The current European labelling information is the following: “Paediatric use: The experience in children is limited. Of 7 patients less than 18 years of age (range 5 to 16 years) treated with TRISENOX at the recommended dose of 0.15 mg/kg/day, 5 patients achieved a complete response. Safety and effectiveness in paediatric patients under 5 years of age have not been studied.”

On December 12th, 2008, the Marketing authorisation holder (MAH) submitted one completed paediatric study (CTI 1059) for Trisenox, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Trisenox and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- a phase I trial and pharmacokinetic study (T99 080): Results are only available as a publication
- a phase III study : Preliminary results are only available as a press release and an abstract.

Documents are evaluated separately in section II.3.2 and benefit risk ratio is discussed in section II.3.4.

1. SCIENTIFIC DISCUSSION

1.1. Information on the pharmaceutical formulation used in the clinical studies

In CTI 1059 study, the investigational product was arsenic trioxide injection (Trisenox®) supplied by Cell Therapeutics, Inc (CTI). In T99 080 study, Trisenox® was supplied by the cancer therapy evaluation Program, NCI (Bethesda, MD).

1.2. Non-clinical aspects

The MAH did not submit non-clinical studies.

1.3. Clinical aspects

1.4. Introduction

First, Cephalon submitted, in December 2008, a phase I trial publication, a phase II clinical study report, a phase II press release and a set of publications.

The MAH submitted report for CTI 1059: Phase II Study of Arsenic Trioxide in Neuroblastoma and Other Pediatric Solid Tumors. The objectives of this study were to determine response rates of patients treated with arsenic trioxide for relapsed or refractory neuroblastoma or other poor-prognosis paediatric solid tumors and to determine toxicity of arsenic trioxide in a patient population that has been heavily treated with agents different than those used in the treatment of acute promyelocytic leukemia (APL).

The MAH submitted a publication for Study T99 080 Phase I trial and pharmacokinetic of arsenic trioxide in children and adolescents with refractory or relapsed acute leukemia including acute promyeolocytic leukemia or lymphoma, a collaborative study of the pediatric oncology branch, national cancer institute and the children's oncology group.

The MAH submitted an abstract and a press release for CALGB C9710, Consolidation with arsenic trioxide (As_2O_3) significantly improves event-free survival (EFS) and overall survival (OS) among patients with newly diagnosed acute promyelocytic leukemia (APL).

This randomized phase III study was conducted by 5 cooperative groups (CALGB, ECOG, SWOG, COG, NCIC-CTG). It was designed to evaluate the benefit and toxicity of two 25-day courses of As_2O_3 as first post-remission therapy for newly diagnosed patients with APL.

Secondly, Cephalon submitted, in March 2009, a cover letter and a clinical overview, the conclusion of which is reported below:

Arsenic trioxide (TRISENOX) at 0.15 mg/kg/day (approved posology in EU and US) has an acceptable safety profile in children and adolescents with relapsed or refractory leukaemia. Limiting toxicity observed is similar in terms of frequency and characteristics to previously published data in adult patients.

As for adult patients, careful monitoring of QTc interval and correction of hypomagnesaemia, hypokaliaemia, or hypocalcaemia are warranted.

For obese children and adolescents, TRISENOX dosing using ideal body weight should be considered.

In children with relapsed or refractory APL, morphologic and cytologic responses can be achieved which places TRISENOX as the most effective agent in this setting.

Although the small number of children and adolescents treated (from 2 to 18 years), the response rate was found similar to the response rate in adults. TRISENOX can be considered as an appropriate treatment of relapsed or refractory APL paediatric population.

However, no efficacy was observed in Neuroblastoma and non-APL leukaemia.

Given the rarity of the relapsed/refractory Acute Promyelocytic Leukemia (APL) disease in paediatric population, limited information is provided in the current SmPC in this population, ranging from 5 to 16 years. Based on the new information available from the T-99-080 study, we propose to amend the SmPC to include updated information on efficacy and safety on Trisenox in paediatric patients ranging from 4 to 18 years. It is proposed to amend the following sections of the SmPC:

- Section 4.1: to broaden the current indication to paediatric patients in addition to adult patients,

- Section 4.2: to update the paediatric use section of the posology with the new safety and efficacy information available from the T-99-080 study.

1.5. Clinical studies

CTI 1059: PHASE II STUDY OF ARSENIC TRIOXIDE IN NEUROBLASTOMA AND OTHER PEDIATRIC SOLID TUMORS.

Cephalon's summary

- Description

This phase II study was conducted from April 2001 to June 2004 at Memorial Sloan-Ketting Cancer Center, New York.

- Methods

  - Objective(s)

The objectives of this study were to determine response rates of patients treated with arsenic trioxide for relapsed or refractory neuroblastoma or other poor-prognosis pediatric solid tumors and to determine toxicity of arsenic trioxide in a patient population that has been heavily treated with agents different from those used in the treatment of acute promyelocytic Leukemia (APL).

  - Study design

Patients were treated with arsenic trioxide 0.25 mg/kg/day IV for 5 consecutive days, followed by no treatment for 2 days, then treatment for another 5 consecutive days, then no treatment for 14 days. If patients had no evidence of disease progression, remained medically stable, and had not experienced grade 4 drug-related toxicity, they could be retreated for up to 6 cycles.

Disease response was assessed after every 3 cycles of treatment and then, if the disease had responded, every 2-3 months through 1 year after completion of arsenic trioxide. Response

was measured according to the tumor in question, including bone marrow aspirations and biopsy specimens from bilateral iliac crests; CT or MRI of primary site and of potential sites of metastases (e.g., lungs); scintigraphic studies such as PET scan, bone scan, gallium scan, or MIBG scan; or biochemical tumor markers (e.g., serum alpha-fetoprotein, urine catecholamines).

Toxicities were assessed from the time of first study treatment until the follow-up visit 4 weeks after the last dose of study drug according to the NCI Common Toxicity Criteria (CTC), Version 2.

Baseline assessments were relevant history and physical examination (including tumor measurements), neurological examination, complete blood count, clinical chemistry, serum or urinary human chorionic gonadotropin assay (or other suitable test to assess pregnancy status) in women of child-bearing potential, other blood tests as needed to assess disease status (e.g., serum lactate dehydrogenase [LDH]), electrocardiogram (ECG), and chest X-ray. Complete blood count and clinical chemistry were assessed before each cycle and at end of weeks 1 and 2. Serum sodium, potassium,

chloride, bicarbonate, magnesium, calcium were assessed each day of treatment with ATO. ECG was performed in each treatment week and at the end of each 4-week cycle.

The study was to employ the SWOG two-stage design27 to evaluate the activity and safety of arsenic trioxide in patients with neuroblastoma and other poor-risk pediatric solid tumors. However, the study was ended prematurely and the first stage was not completed in any of the 3 subgroups.

- Study population /Sample size

This was designed as a 2-stage study in which 15 patients would be enrolled in each of 3 subgroups (neuroblastoma patients with progressive disease at study entry, neuroblastoma patients with stable disease at study entry, and patients with diagnoses other than neuroblastoma) in the first stage, with an additional 25 patients enrolled in any subgroup if a response was seen. If no response was seen in the 15 patients, the trial would be terminated for that subgroup but would continue to enroll patients in the other subgroups.

Twenty patients were enrolled and received study drug: 8 had progressive neuroblastoma, 8 had stable neuroblastoma, and 4 had diagnoses other than neuroblastoma.

Eligible patients had measurable or evaluable neuroblastoma or other pediatric solid tumor.

Additional criteria were:

• Age ≤40 years (added in protocol amendment 1)

• Relapse from or resistance to standard anticancer therapy and/or lack of standard therapy known to be beneficial in the underlying disease.

• Serum creatinine ≤2.5 times the upper limit of normal.

• Serum bilirubin ≤2.5 times the upper limit of normal.

• Patients with absolute QT interval >460 msec in the presence of adequate serum potassium and magnesium values were excluded.

• Patients with pre-existing neurotoxicity/neuropathy of grade 2 or greater were excluded in the original protocol. As of protocol amendment 2, patients with brain tumors who had stable neurological deficits were eligible to enroll.

- Treatments

Arsenic trioxide 0.25 mg/kg/day was administered as an intravenous infusion.

Patients were treated for up to 6 cycles. Patients were removed from study treatment if they had evidence of disease progression, were medically unstable, or experienced grade 4 drug-related toxicity.

- Outcomes/endpoints

Criteria for assessment of disease response were based on the patient's diagnosis at study entry. For patients with neuroblastoma, disease response was assessed using the International Neuroblastoma Response Criteria, with assessment dependent on whether the patient entered the study with progressive or stable disease. For patients with PD at study entry, response to treatment was defined as SD or better after 3 cycles of treatment. For patients with refractory but non-progressing disease (defined as SD or better), response to treatment was defined as PR or better after 3 cycles of treatment or more than 12 weeks from the start of the study, or as SD or better after 6 cycles or more than 24 weeks from the start of the protocol.

For patients with other solid tumors (non-neuroblastoma), disease response was assessed using RECIST criteria to evaluate a set of target lesions identified prior to treatment with study drug.

Disease response for all patients was assessed after every 3 cycles of treatment and then, if the disease had responded, every 2-3 months through one year after completion of arsenic trioxide treatment with bone marrow aspirations and biopsy specimens from bilateral iliac crests; CT or MRI of primary site and of potential sites of metastases (e.g., lungs); scintigraphic studies such as PET scan, bone scan, gallium scan, or MIBG scan; or biochemical tumor markers (e.g., serum alpha-fetoprotein, urine catecholamines).

Toxicities were assessed from the time of first study treatment until the follow-up visit 4 weeks after administration of the last dose of study drug according to the NCI Common Toxicity Criteria (CTC), Version 2. Complete blood count and clinical chemistry were assessed before each cycle and at end of weeks 1 and 2. Serum sodium, potassium, chloride, bicarbonate, magnesium, calcium were assessed each day of treatment with ATO. ECG was performed in each treatment week and at the end of each 4-week cycle.

- Statistical Methods

The study employed the SWOG two-stage design, in 3 sub-groups of patients: 1) neuroblastoma patients with progressive disease at study entry, 2) neuroblastoma patients with stable (refractory, non-progressive) disease at study entry, and 3) patients with diagnoses other than neuroblastoma. Probability of response and associated 95% confidence interval outlined in the protocol were not calculated because the 3 subgroups did not enroll to the planned level. Demographic data and safety variables will be summarized by descriptive statistics. Response is listed by patient.

➢ Results

- Recruitment/ Number analysed

Twenty patients were enrolled and treated in this study; 8 had progressive neuroblastoma, 8 had stable neuroblastoma, and 4 had diagnoses other than neuroblastoma. Mean age was 12 years and ranged from 4 to 36 years. Most patients (80%) were Caucasian and had neuroblastoma (80%). Mean time from diagnosis to the first dose of study was 3 years. Three patients each received 6 cycles and completed the study. Sixteen patients were discontinued due to disease progression and one patient withdrew consent after cycle 1.

- Efficacy results

Of the 19 patients evaluated for efficacy in this pediatric tumor population with historically poor prognosis, 1 patient with neuroblastoma had a mixed response at 2 consecutive assessments on days 85 and 157and 2 patients had no response at the end of the study. However, the two patients that had no response at the end of the study had not shown disease progression for 5.5 and 6 months respectively. The remaining 16 patients had progressive disease.

- Safety results

The most common adverse events were pyrexia (60%) and nausea, vomiting, cough and cancer pain (each 35%). The most common adverse events attributed by the investigators to study drug were electrocardiogram QT prolonged (15%) and headache, nausea, and vomiting NOS (each 10%). Serious adverse events were reported frequently (75%). The most commonly reported serious adverse events

were pyrexia (50%), neutropenia (15%) followed by herpes zoster, pneumonia, cancer pain, leukopenia, diarrhea, and dehydration (10%).

QT prolongation was closely monitored as a possible drug-related adverse event in this study.

Four (20%) patients had prolonged QT intervals, 3 of grade 1 severity and 1 of grade 3. None of these events led to patient discontinuation.

Hematologic laboratory evaluations revealed frequent grade 3 abnormalities in haemoglobin and grade 3 and 4 abnormalities in platelets and neutrophils. Clinically significant grade shifts were observed in all 3 analytes that did not fully recover by the end of treatment. The data suggest that ATO may be associated with myelosuppression although the extent of marrow suppression present at baseline in many of these poor prognosis, refractory patients indicates that the underlying advanced malignancy and its progression was likely a more significant factor.

Chemistry laboratory evaluations revealed mild to moderate elevations in glucose during the study, not unexpected with ATO. They were transient and easily managed. Electrolyte abnormalities were observed but were generally transient and likely related to gastrointestinal toxicity. Mild to moderate shifts in ALT and AST occurred during the study that did not fully resolve by the end of treatment suggesting that ATO may be associated with an increase in transaminases. No abnormalities in renal function were observed.

No meaningful changes in vital signs were seen over time. Marked abnormalities were generally related to comorbid diseases, their treatments, or concurrent adverse events.

There were four deaths within 30 days of the last study treatment, all related to progression of disease.

In conclusion, ATO administered for 5 days followed by 2 days of no treatment, another 5 days of treatment and then 14 days of no treatment up to a maximum of 6 cycles was generally well tolerated in patients with relapsed or refractory neuroblastoma and other poor prognosis pediatric solid tumors.

Rapporteur's comments:

CTI-1059 study enrolled children and adult patients with neuroblastomas and other paediatric solid tumours. These indications are not in the scope of the marketing authorisation, and the dose used (0.25 mg/kg/day) is superior to the recommended dose in APL (0.15 mg/kg/day).

Off the 20 patients included, only 16 are paediatric patients. Presented data from these 16, cover all ranges of age from 4 to 18 years.

One patient with neuroblastoma had a mixed response seen at 2 consecutive assessments (days 85 and 157). He completed the maximum allowed 6 cycles of treatment on this study.

Two patients with neuroblastoma had no response (NR) and completed the maximum allowed 6 cycles of treatment.

All of the remaining 16 patients that were evaluated for efficacy had progressive disease.

With reference to efficacy, no data are available to each paediatric group. Only 3 patients received the whole treatment (6 cycles)

The only relevant information is that the median number of arsenic trioxide doses administered was 15 (3 x 5 days) and the mean cumulative dose was 127.77 mg/m2 (128.31 mg).

Regarding the safety profile of ATO in the setting of neuroblastoma, based on the data provided, the nature of the most common adverse events in children and adolescents seems equivalent to that of adults. However, the higher dosage used in this trial (0.25 mg /kg) precludes any comparison with regards to the study drug related adverse events that seem higher in this paediatric population.

Four patients (20%) died, within 30 days of last dose, of disease progression.

Discontinuation of treatment is attributed to adverse events secondary to disease progression.

Since only 3 patients completed the treatment, the extent of treatment related adverse event is not assessable.

Furthermore, in this paediatric population subject to growth, and given the high dosage used, the estimation of cumulative toxicity is of great concern.

Eventually, an extension of indication and/or an update of the posology, as requested in the clinical overview, should be evaluated as part of a corresponding future type II variation and not as part of the art. 45 procedure.

STUDY T99 080: PHASE I TRIAL AND PHARMACOKINETIC OF ARSENIC TRIOXIDE IN CHILDREN AND ADOLESCENTS WITH REFRACTORY OR RELAPSED ACUTE LEUKEMIA INCLUDING ACUTE PROMYEOLOCYTIC LEUKEMIA OR LYMPHOMA, A COLLABORATIVE STUDY OF THE PEDIATRIC ONCOLOGY BRANCH, NATIONAL CANCER INSTITUTE AND THE CHILDREN'S ONCOLOGY GROUP

Cephalon's summary

- Description

This study was a dose-escalation Phase I study in children and adolescent with relapsed or refractory leukemia.

- Methods

Patients with relapsed APL were administered with the approved TRISENOX dose of 0.15 mg/kg, and 3 dose levels (0.15, 0.1 and 0.25 mg/kg) were planned for other leukemia or lymphoma patients. TRISENOX was administered intravenously over 2 hours each day for 5 consecutive days for 4 weeks (20 doses), with a 2-week break between treatment and a maximum of 3 cycles. The objectives of the study were to evaluate the safety of TRISENOX at 0.15mg/kg in children with APL and to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of TRISENOX in non-APL patients, and to study the pharmacokinetics of TRISENOX in children.

Twenty-four paediatric patients with recurrent or refractory leukaemia were enrolled including 14 patients with refractory APL and 10 with leukaemia, non-APL, or lymphoma. Patients were from 2 to 21 years old with a median age of 13 years.

Within the 14 patients with APL, 1 patient was found not to be eligible for the study after inclusion. This patient did not experience toxicity attributed to TRISENOX, but other data from this patient has been excluded from the report. Within the 10 patients with other leukaemia or lymphoma enrolled in the dose escalation portion of the study, 4 had progressive disease prior to completing cycle 1 and were inevaluable; 4 patients were administered with TRISENOX 0.15 mg/kg per day, and 6 with 0.2

mg/kg per day. Of the 19 evaluable patients for toxicity, 2 received less than 1 cycle, 8 received 1 cycle, 3 received 2 cycles, and 6 received the maximum 3 cycles as planned in the protocol. All patients who received more than 1 cycle had APL.

PK parameters were derived on 10 patients who received 0.15 mg/kg per dose, 2 patients treated at 0.2 mg/kg per dose and 2 patients dosed according to ideal body weight (0.07-0.1 mg/kg of actual body weight per dose).

- Results

Morphologic complete response (CR) was achieved in 85% (11 out of 13) of patients with APL. This response rate is similar to the response rate in adults.

No response was observed in non-APL patients.

Dose limiting toxicity was reported in 2 out of 15 patients at 0.15 mg/kg per day, and in 2 out of 4 patients at 0.2 mg/kg per day. This included QTc prolongation, pneumonitis, neuropathic pain, and pancreatitis. The QTc prolongation (grade 1 in 2 patients, one patient treated at 0.15 mg/kg and one at 0.2 mg/kg) normalized upon cessation of TRISENOX treatment and correction of electrolyte abnormalities, if present. Frequent non-dose-limiting toxicities included elevated serum hepatic transaminases (37%), nausea/vomiting (26%), abdominal pain (10%), constipation (16%), hypomagnesemia (26%), hypocalcemia (26%), hyperglycemia (26%), dermatitis (26%), infection (16%), and headache (16%). The acute toxicity profile of TRISENOX in children is similar to that observed in adults.

Rapporteur's comments:

The results of this study are provided in this application in the form of a publication in Blood, dated 15 January 2008.

24 children with recurrent or refractory leukaemia were enrolled between July 2000 and January 2005.

Within the 14 patients with APL, 13 were evaluable for efficacy. It should be noted that the median age for this subpopulation was 17 years (4-21 years).

In children with relapsed or refractory APL, morphological complete response was achieved in 11 out of 13 patients (85%). CR has been achieved with 20-30 doses of arsenic. Cytogenetic response occurred in 9 out of 11 patients but 70 doses were required to achieve negative RT-PCR.

Even though the efficacy results on children with APL seem encouraging, the form of this submission does not allow a fully valuable assessment.

Since the objective of this study was to evaluate the tolerability of arsenic trioxide in children with APL and to determine DLT and MTD in children with non APL leukaemia, this results could be of interest. Moreover, pharmacokinetic data from ten children who received ATO 0.15mg/kg/dose, two children treated at 0.2 mg/kg/dose, and two patients dosed according to ideal body weight (0.07-0.1 mg/kg of actual body weight/dose) should be provided. Interestingly, two patients who were obese (BMI>30) and who were dosed based on ideal body weight suffered most of the significant toxicities observed on subsequent treatment cycles. Given the existing association between diagnosis of acute promyelocytic leukemia in patients and increased body mass index with acute myeloid leukemia (Estey et al., Leukemia 1997), these important data should be further investigated.

The toxicity profile in children seems similar to previously published data in adult patients. However the data alert on the need for careful monitoring of QTc interval and correction of hypomagnesaemia, hypokaliaemia or hypocalcaemia.

Long term toxicity especially in infants and adolescents is a concern. As noticed by the MAH, this trial was not powered to address this issue.

Indeed, the population targeted fall into the frame of Trisenox current indication (recurrent or refractory APL). Hence, the MAH intends to update section 4.2 of Trisenox SPC with the safety and efficacy information available from T99-080 study in paediatric patients. The Rapporteur considers that, to form a robust basis of such an update, the MAH should provide the results of this trial as a clinical study report including an update of responding patients, to allow the request for a type II variation.

CALGB C9710, CONSOLIDATION WITH ARSENIC TRIOXIDE (AS_2O_3) SIGNIFICANTLY IMPROVES EVENT-FREE SURVIVAL (EFS) AND OVERALL SURVIVAL (OS) AMONG PATIENTS WITH NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA (APL).

- Description

The results of this study are provided in this application in the form of a press release and an abstract given below.

Consolidation with arsenic trioxide (As2O3) significantly improves event-free survival (EFS) and overall survival (OS) among patients with newly diagnosed acute promyelocytic leukemia (APL): North American Intergroup Protocol C9710.

Bayard L. Powell, MD1, Barry Moser, MD1, Wendy Stock, MD[1], Robert E. Gallagher, MD[2], Cheryl L. Willman, MD[3], Steven Coutre, MD3, James H. Feusner, MD[4], Frederick R. Appelbaum, MD[3], Martin S. Tallman, MD[2] and Richard A. Larson, MD[1]

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***Background**: This randomized phase III study was designed to evaluate the benefit and toxicity of two 25-day courses of As2O3 as first post-remission therapy for newly diagnosed patients with APL.* ***Methods**: Adult patients were randomized to receive 2 courses of As2O3 (0.15 mg/kg/d for 5d each wk for 5 wk) as a first consolidation if they achieved remission (CR or PR) after induction with oral tretinoin (ATRA; 45 mg/m2/d), daunorubicin (50 mg/m2 IV x 4d), and cytarabine (200 mg/m2 CIV x 7d); by study design, all but 2 children were assigned to the non-As2O3 arm. Subsequent consolidation on both arms included 2 courses of ATRA (45 mg/m2 x 7d) + daunorubicin (50 mg/m2 x 3d; 2d for age < 15 yr). CR patients were then randomized to 1 yr of ATRA maintenance (7d repeated every other wk) with or without 6-mercaptopurine (daily) + methotrexate (weekly).* ***Results**: 518 adults (15-79 yr) and 64 children (<15 yr; 11%) with untreated APL were enrolled by 5 cooperative groups (CALGB, ECOG, SWOG, COG, NCICCTG). Eligibility required demonstration of PML-RARA in one of 3 central labs; 37 adults and 7 children were ineligible and not included in the analyses. Patient characteristics and toxicity data have been reported (ASH 2006; Blood 108:171a).*
Median follow up is now 29 mos. Overall CR rate for adults was 89% and did not differ by treatment arm; CR rate for children was 89%. There were 41 deaths (8%) within 60 days. EFS, the primary endpoint, was 77% at 3 yrs on the As2O3 arm (median, not reached) compared to 59% at 3 yrs on the standard arm (median, 63 mos; p=0.0013).
Overall, 84% of adults were alive at last follow up. OS was 86% at 3 yrs on the As2O3 arm compared to 77% at 3 yrs on the standard arm (medians not reached; p=0.029); EFS and OS for pediatric patients did not differ statistically from the adult arm without As2O3. Among 452 CR pts, there have

been only 71 post-CR events (16%) so disease-free survival has not yet been analyzed by treatment arm.

***Conclusion**: The addition of 2 courses of As2O3 consolidation following remission induction significantly improves EFS and OS in adults with APL.*

Rapporteur's comments:

Between June 1999 and March 2005, 582 patients were enrolled on this study of which 64 children with untreated APL. This study was randomised but all but 2 children were assigned to the non AS_2O_3 arm, meaning that this study was not designed to give statistical evidence of efficacy or safety in children.

No information regarding paediatric population has been provided in the last PSUR 7 covering the period from March 2006 to September 2008. The MAH is asked to provide the final results of CALGB C9710 study as soon as possible.

In any case, the form of this submission does not allow any assessment. The need for the submission of a type II variation to broaden the indication to children will be assessed at this time.

Publications

25 publications from 1994 to 2006 were retrieved by Cephalon.

Rapporteur's comments:

Article 45 refers to the obligation for the MAH to submit any studies for an authorised product, including those with both adult and paediatric patients. In such, the literature review is not an extensive and updated one.

See examples below.

Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet.

Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, Naoe T, Lengfelder E, Büchner T, Döhner H, Burnett AK, Lo-Coco F. Blood. 2009 Feb 26;113(9):1875-91. Epub 2008 Sep 23

Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin.

Ravandi F, Estey E, Jones D, Faderl S, O'Brien S, Fiorentino J, Pierce S, Blamble D, Estrov Z, Wierda W, Ferrajoli A, Verstovsek S, Garcia-Manero G, Cortes J, Kantarjian H.

J Clin Oncol. 2009 Feb 1;27(4):504-10. Epub 2008 Dec 15.

A comprehensive review of acute promyelocytic leukemia in children.

Mantadakis E, Samonis G, Kalmanti M.

Acta Haematol. 2008;119(2):73-82. Epub 2008 Feb 20.

Mobilization of PML-RARA negative blood stem cells and salvage with autologous peripheral blood stem cell transplantation in children with relapsed acute promyelocytic leukemia.

Termuhlen AM, Klopfenstein K, Olshefski R, Rosselet R, Yeager ND, Soni S, Gross TG.

Pediatr Blood Cancer. 2008 Oct;51(4):521-4.

Retrospective analysis of 65 Chinese children with acute promyelocytic leukemia: a single center experience.

Zhang L, Zhao H, Zhu X, Chen Y, Zou Y, Chen X.

Pediatr Blood Cancer. 2008 Aug;51(2):210-5

Arsenic trioxide, thalidomide and retinoid acid combination therapy in higher risk myelodysplastic syndrome patients.

Zheng WL, Zhang GS, Xu YX, Shen JK, Dai CW, Pei MF.

Leuk Res. 2008 Feb;32(2):251-4. Epub 2007 Oct 24

1.6. Discussion on clinical aspects

Formal aspects

New post-approval paediatric information consists of 2 main trials, one in solid tumours and one in leukaemia, as reported below:

- The CTI-sponsored CTI-1059 phase II trial that enrolled 16 paediatric patients from 4 to 17 years with neuroblastomas and other paediatric solid tumours. The clinical study report (CSR) was finalized in October 2005, and then upgraded by an Addendum 1 version signed in December 2006 which cancelled and replaced the initial CSR. The MAH provided the Rapporteur with this addendum which forms the basis for the assessment of paediatric data.

- A US study (T-99-080), sponsored by the American National Cancer Institute (NCI), enrolled 24 paediatric patients amongst them 14 with refractory APL and 10 with leukemia, non-APL, or lymphoma. No formal CSR is available. The results displayed in a publication do not provide the material for an assessment.

In addition, preliminary data from CALGB C9710 study are submitted in the form of a press release and an abstract. But final data are not yet available.

Substantial aspects

Although neuroblastomas and other paediatric solid tumours are not in the scope of the marketing authorisation indication for trisenox, the results of CTI-1059 study give information on paediatric population.

The Rapporteur acknowledges that because of the rarity of the disease in the paediatric population, no data are available to each paediatric group as per the International Conference on Harmonisation (ICH) E11 Clinical investigation of medicinal products in the paediatric population (20 July 2000).

If the MAH intends to update SPC in view of results of T 99-080 trial, he should provide the clinical study report as a material for type II variation.

Regarding CALGB C9710 study, the MAH states that no conclusion is expected on paediatric population from this study since only 2 children have been treated with arsenic trioxyde. Even if this study does not sound informative for the paediatric patients, it is in the list of clinical specific obligations. The MAH is requested to submit it to the EMEA as soon as available.

2. Rapporteur's Overall Conclusion and recommendation

As a general comment and given the rarity of the described conditions, duplicate reports of cases cannot be excluded and this should be addressed when formal type II variation request will be submitted.

In form and substance this application is insufficient.

For the time being, and considering the fragmented collection of paediatric data, it is impossible to decide whether a formal type II variation with indication modification should be acceptable or no modification is needed. This must be based on assessment of reliable, updated and exhaustive data.

The full efficacy data and consequently the overall benefit risk ratio of the proposed new broader indication will be assessed as part of a future type II variation (extension of Indication).

However, Trisenox was authorised in 2002 under exceptional circumstances and is an orphan medicinal product..

Importantly, no information regarding paediatric population has been provided in the last PSUR 7 covering the period from March 2006 to September 2008. The MAH is asked to provide the final results of CALGB C9710 study as soon as possible. Furthermore, pharmacokinetic data from STUDY T99 080 should be provided.

Comments were received from member states: MS1 and MS2 endorse the Rapporteur's assessment report.