Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Zavedos , Zavedos oral (different strengths each, in the RMS DE) Idarubicin

DE/W/024/pdWS/001

Rapporteur:	Germany (DE)
Finalisation of procedure (Day 120)	22.10.2013
Date of finalisation of PAR	04.12.2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section X
INN (or common name) of the active substance(s):	idarubicin
MAH (s):	See section X
Pharmaco-therapeutic group (ATC Code):	Anthracyclines and related substances (L01DB06)
Pharmaceutical form(s) and strength(s):	injection solution (10 mg/10 ml; 20 mg/20ml) powder and solvent for reconstitution of an injection solution (5, 10, and 20 mg) hard capsules (5, 10, and 25 mg)

I. EXECUTIVE SUMMARY

Originally, SmPC and PL changes were proposed in sections 4.1, 4.2, 4.4, 5.2 (SmPC) as well as sections 1 and 2 (PL).

Day 90 update

In response to the 1st LoQ, SmPC and PL changes are proposed in sections 4.1, 4.2, 4.4, 5.2 (SmPC) as well as sections 1, 2, and 3 (PL).

Day 91 update

In response to the 2nd LoQ, SmPC and PL changes are proposed in sections 4.1, 4.2, 4.4, 5.2 (SmPC) as well as sections 1, 2, and 3 (PL).

New study data: section(s) Indication (sec. 4.1) and posology (section 4.2), and corresponding sections of PL reflecting result of the sequence of BMF trials (AML BFM 93 - doi:10.1038/sj.leu.2403920 as well as Leukemia 15, 348–354, 2001 or http://www.nature.com/leu/journal/v15/n3/pdf/2402046a.pdf , AML-BFM 98 - http://abstracts.hematologylibrary.org/cgi/content/abstract/104/11/1793, AML-BFM 2004 - http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/181), sec. 5.2 adding (i.v. and oral) paediatric ADME data based on a literature review.

New safety information: addition of specific sensitivity to anthracyclin induced cardiotoxicity in childhood to section 4.4.

Paediatric information clarified: sections 4.1, 4.2, 4.4

Please note that the new proposals are made only in relation to sec. 5.2 of the SmPC. PL submitted on request of RMS on September 19, 2013 is identical to that which had been submitted in response to 1st LoQ.

In particular, the MAH is maintaining the original (but by RMS not recommended) paediatric ALL indication, has not made proposals for separating PIs of hard capsules and injection solution, and has not taken the opportunity to add non-confirmed information concerning ALL in childhood to sec. 5.1 of the SmPC.

Summary of outcome

☐ No change

☒ Change

☒ New indication: sections 4.1, 4.2

II. RECOMMENDATION

Original recommendation

The proposed (additional) indication(s) in ALL should not be granted.
A not proposed indication in AML of childhood should be granted, and the data on file of the MAH should be updated accordingly.
Variations of sections 4.1, 4.2, 4.4, 5.3 (SmPC) as well as sections 1 and 2 (PL) should be performed in the national SmPCs and PLs of the involved MS once this article 45 has been concluded.

Since the (national) SmPCs (and PLs) are not harmonized, the conduct of a article 30 procedure is highly recommended by the RMS of this article 45 procedure.

Former Day 90 update of (preliminary) recommendation

The data submitted by the MAH with the responses to the (first) Draft Paediatric Assessment Report, and the new proposals for SmPC and PL require an additional List of Questions as well as a further discussion round of the SmPC/PL proposals.

The following are recommendations of the RMS for final SmPC/PL proposals/final recommendation to all member states involved:

1. Proposals for the SmPC and PL hard capsules should be separated from proposals for the SmPC and PL foreseen for injection solutions and powders and solvents for reconstitution of injection solutions.
2. No indication in childhood shall be granted to the hard capsuled.
3. No monotherapy indication in childhood shall be granted.
4. No indication in ALL shall be granted.
5. Non-confirmatory information on paediatric use outside of the AML indication may be added to sec. 5.1 of the SmPC. The MAH may submit adequate proposals.

In Detail:

SmPC (for injection solutions and powders and solvents for reconstitution of injection solutions only; day 90 proposals of the MAH bold and struck through, proposals of the RMS bold and underlined)

4. 1 Therapeutic indications

Idarubicin is indicated **as part of a combination therapy** for first-line treatment **(remission induction)** of children with acute myeloid leukemia (AML**) ~~or for remission induction in paediatric patients with relapsed or refractory AML.~~**

~~Idarubicin is indicated as second-line treatment in children with Acute lymphocytic leukemia (ALL)~~

4.2 Posology and method of administration

Intravenous Administration
AML

~~**Monotherapy:**~~

~~**In children with AML, the recommended single-agent intravenous dose is 10-12 mg/m^2 IV (over 10—30 minutes) once daily for 3 days; repeat every 3 weeks.**~~

Combination therapy:

In children with AML the recommended dose **in combination with Ara-C** is 10**-12** mg/m^2 IV daily for 3 days by slow IV **injection** ~~**in combination with Ara-C**~~.

Assessor's comment

Dose range recommended by RMS. Proposal needs further discussion with MAH and CMS. Actually there are indications that 10 mg/m^2 may be both safer and more efficacious than the 12 mg/m^2 used in most protocols.

~~**ALL**~~

~~**Monotherapy:**~~

~~**In children with ALL, the recommended single-agent intravenous dose is 10 mg/m^2 daily for 3 days.**~~

~~**Combination therapy:**~~

~~**Although in clinical practice the use of anthracyclines in combination for induction therapy in children with ALL is well documented as a forth agent, particularly for high**~~

~~**risk patients, dosage regimens vary according to condition and individual clinical protocols.**~~

NOTE: These are general guidelines. Refer to individual protocols for exact dosage.

~~Oral Administration~~

~~**AML and ALL**~~

~~**Monotherapy:**~~

~~**In children with AML and ALL, the recommended oral dose schedule is 30 mg/m^2 daily for 3**~~

~~**days as a single agent**~~

~~**Combination therapy:**~~

~~**In children with AML and ALL, the recommended oral dose is between 15 and 30 mg/m^2 daily for 3 days in combination with other antileukemic agents.**~~

~~**A maximum cumulative dose of 400mg/m^2 for oral idarubicin is recommended.**~~

~~**NOTE: All of these dosage schedules should, however, take into account the hematological status of the patient and the dosages of other cytotoxic drugs when used in combination.**~~

Assessor's comment

To add, within in a separate SmPC for the tablets a maximum cumulative oral dose in children of 400 mg/m^2 could make some sense but not in the separate SmPC for solutions for injections discussed here.

4.4 Special warnings and precautions for use

In infants and children there appears to be a greater susceptibility to anthracycline-induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed.

4.8 Undesirable effects

Assessor's comment

An appropriate statement that undesirable effects in children are approximatively the same as in adults (except greater susceptibility to anthracycline-induced cardiac toxicity) shall be added.

5.1 Pharmacodynamic properties

Assessor's comment

See general recommendation # 5 above

5.2 Pharmacokinetic properties

Paediatric population:

Pharmacokinetic measurements in 7 pediatric patients receiving intravenous idarubicin in doses ranging from ~~**15 to 40 mg/m^2/3 day course of treatment**~~ **5 to 13.3 mg/m^2 daily for three days**, showed a median idarubicin half life of 8.5 hr (range: 3.6 – 26.4 hr). The active metabolite, idarubicinol, accumulated during the 3 day**s of the course** ~~**therapy**~~, exhibiting a median half life of 43.7 hr (range: 27.8-131 hr). In a separate study, pharmacokinetic measurements in 15 pediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2~~**/3 day course of treatment**~~ **daily for three days**, showed a median terminal half life of idarubicin of 9.2 hr (range: 6.4-25.5 hr). Significant accumulation of idarubicinol was seen over the 3 day**s of the course.** ~~**treatment period**~~

Assessor's comment

A statement on comparative PK children vs. adults shall be added. Relation of clearance, volume of distribution, and elimination/terminal half-life adults vs. children, is however still not clear (see proposed 2nd LoQ).

PL (for injection solutions and powders and solvents for reconstitution of injection solutions only; day 90 proposals of the MAH bold and struck through, proposals of the RMS bold and underlined)

1. What Product X is and what it is used for

This medicine can be use alone or in combination with other anti-cancer drugs

• ~~**A**~~**a**s first-line treatment of children with acute myeloid leukemia (AML) ~~**or for remission induction in relapsed or refractory paediatric patients.**~~

• ~~**For the treatment of relapsed and/or refractory acute lymphocytic leukemia (ALL) in paediatric patients.**~~

~~**Oral administration is used when intravenous administration cannot be used.**~~

2. Before you take Product X

Take special care with Product X

Before starting and during <Product X> treatment, regular checks of your blood, liver, kidneys and heart will be performed. Infants and children seem to be more sensitive to the cardiotoxicity of antracyclins; therefore, it is necessary to make long-term, periodic cardiac function examination in these patients.

3. How to take Product X

Children

Injection

AML

• ~~**If the child is receiving idarubicin alone the recommended dosage is 10mg to 12mg/m², administered into a vein, over a 10 to 30 minute period, once a day. This is repeated every three weeks.**~~

• If the child is receiving idarubicin plus other antileukemic medicines the recommended dosage is 10 **to 12** mg /m², administered slowly into a vein once a day. This is repeated every three weeks.

Assessor's comment

See assessor's comment on dose range in sec. 4.2 of the SmPC

~~**ALL**~~

~~- If the **child is receiving idarubicin alone the recommended dosage is 10mg/m², administered slowly into a vein once a day for 3 days.**~~

~~- The combination therapy for ALL is calculated by your doctor. Your doctor after careful **consideration will advise you on the most suitable dosing regimen based on your circumstances.**~~

~~**Capsule**~~

~~**AML and ALL**~~

~~- If the child is receiving idarubicin alone the recommended dosage is 30 mg/m2 daily **given orally for 3 days as a single agent**~~

~~- If the child is receiving idarubicin plus other an~~**tileukemic medicines the**

Final recommendation

Comments on the assessment of the 2nd request for supplementary by the RMS plus resulting proposals for SmPC/PL wordings were received by IE, NL, and UK.

All comments endorsed the proposal of the RMS to add a paediatric indication in AML to the PI as proposed.

IE and NL were are rejecting the deletion of ALL indication(s). As to the latter the RMS has to state that no ALL indication has been granted to idarubicin in the RMS (DE). Thus, the RMS considers that the proposals of the RMS were misunderstood by CMSs IE and NL. The RMS DE was proposing to delete sentences from the **request of the MAH to add** to all PIs of the MSs.

Thus, please note that the final recommendation comprises additions only, but **no deletions**, to PIs of the MSs.

Final recommendation after assessment of latest CMSs comments:

Type IB variation to be requested from the MAH by 21.12.2013 adding the following SmPC&PL elements:

1. NAME OF THE MEDICINAL PRODUCT

<[To be completed nationally]>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<[To be completed nationally]>

3. PHARMACEUTICAL FORM

Recommendation valid for intravenous forms only.

<[To be completed nationally]>

FOR INTRAVENOUS PHARMACEUTICAL FORMS ONLY

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<[To be completed nationally]>

Idarubicin, in combination with cytarabin, is indicated for the first remission induction -line treatment of previously untreated children with acute myeloid leukemia (AML).

4.2 Posology and method of administration

Intravenous Administration

<[To be completed nationally]>

Intravenous Administration

AML

Combination therapy:
In children with AML the recommended dose range of idarubicin, in combination with cytarabin, is 10-12 mg/m^2 body surface daily for 3 days by slow intravenous injection.

NOTE: These are general guidelines. Refer to individual protocols for exact dosage.

4.3 Contraindications

<[To be completed nationally]>

4.4 Special warnings and precautions for use

<[To be completed nationally]>

Late (i.e., delayed) Events:

<[To be completed nationally]>

In infants and children there appears to be a greater susceptibility to anthracycline-induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed.

4.5 Interaction with other medicinal products and other forms of interaction

<[To be completed nationally]>

4.6 Pregnancy and lactation

<[To be completed nationally]>

4.7 Effects on ability to drive and use machines

<[To be completed nationally]>

4.8 Undesirable effects

<[To be completed nationally]>

Undesirable effects are similar in adults and children except a greater susceptibility to anthracycline-induced cardiac toxicity of children.

4.9 Overdose

<[To be completed nationally]>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

<[To be completed nationally]>

5.2 Pharmacokinetic properties

<[To be completed nationally]>

Paediatric population:

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2/3 days of treatment, showed a median idarubicin half-life of 8.5 hrs (range: 3.6 – 26.4 hrs). The active metabolite, idarubicinol, accumulated during the 3 days of treatment, exhibiting a median half-life of 43.7 hrs (range: 27.8-131 hrs). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2/ during the 3 days of

treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7 – 16.7 ng/mL at the 40 mg/m^2 dose). The median terminal half-life of idarubicin of was 9.2 hrs (range: 6.4-25.5 hrs). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half-life value of idarubicin after IV was comparable to that following oral administration in paediatric patients.

In adults, following oral administration of 10 to 60 mg/m^2 idarubicin, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4 - 12.65 ng/mL achieved in 1 to 4 hours after dosing. The terminal half-life was 12.7±6.0 hrs (mean±SD). Following intravenous administration of idarubicin in adults, the terminal half-life was 13.9±5.9 hrs , similar to that observed after the oral administration.

Since c_{max} of idarubicin is similar in children and adults following oral administrations, absorption kinetics seem not to differ between adults and children.

Following both oral and IV administrations, the elimination half-life values of idarubicin in children and adults differ:

Total body clearance values of 30-107.9 L/h/m^2 for idarubicin reported for adults are higher than the values of 18-33 L/h/m^2 reported for paediatric populations Although idarubicin has a very large volume of distribution in both adults and children, suggesting that much of the drug is bound to tissues, the shorter elimination half-life and lower total body clearance are not entirely explained by a smaller apparent volume of distribution in children compared to adults.

5.3 Preclinical safety data

<[To be completed nationally]>

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<[To be completed nationally]>

6.2 Incompatibilities

<[To be completed nationally]>

6.3 Shelf life

<[To be completed nationally]>

6.4 Special precautions for storage

<[To be completed nationally]>

6.5 Nature and contents of container

<[To be completed nationally]>

6.6 Special precautions for disposal and other handling

<[To be completed nationally]>

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

[<[To be completed nationally]>

PACKAGE LEAFLET: INFORMATION FOR THE USER

<{(**Invented) name and associated names** (see Annex I) **strength pharmaceutical form**}
[See Annex I - To be completed nationally]>
Idarubicin

Read all of this leaflet carefully before you start taking this medicine.
<[To be completed nationally]>

In this leaflet:
<[To be completed nationally]>

1. What Product X is and what it is used for

[Product X], in combination with cytarabin, is indicated for the first remission induction treatment in previously not treated children with a blood cancer called acute mylogenous leukaemia (AML).

2. Before you take Product X

Do not take Product X
<[To be completed nationally]>

Take special care with Product X
<[To be completed nationally]>
……
Before starting and during <Product X> treatment, regular checks of your blood, liver, kidneys and heart will be performed. Infants and children seem to be more sensitive to the cardiotoxicity of antracyclins; therefore, it is necessary to make long-term, periodic cardiac function examination in these patients.

Taking other medicines
<[To be completed nationally]>

Taking Product X with food and drink
<[To be completed nationally]>

Pregnancy and Breast-feeding
<[To be completed nationally]>

Driving and using machines
<[To be completed nationally]>

Important information about some of the ingredients of Product X
<[To be completed nationally]>

3. How to take Product X

<[To be completed nationally]>

Children

Injection

AML

- If the child is receiving idarubicin plus other antileukemic medicines (cytarabine) the recommended dosage is in the range of 10-12 mg /m², administered slowly into a vein once a day for3 subsequent days. This is repeated every three weeks.

Capsule

If you take more Product X than you should
<[To be completed nationally]>

If you forget to take Product X
<[To be completed nationally]>

If you stop taking Product X
<[To be completed nationally]>

4. Possible side effects
<[To be completed nationally]>

5. How to store Product X
<[To be completed nationally]>

6. Further information

What Product X contains
<[To be completed nationally]>

What Product X looks like and contents of the pack
<[To be completed nationally]>

Marketing Authorisation Holder and Manufacturer
<[To be completed nationally]>

This leaflet was last approved in {MM/YYYY}.
<[To be completed nationally]>

III. INTRODUCTION

Pfizer Ltd., the current MAH of the innovator products of the Zavedos product line, submitted 9 completed paediatric studies for idarubicin, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH proposed the following regulatory action:

It has been suggested adding/amending/harmonizing the NOT harmonized and different European SmPCs of the MSs an adult and a paediatric indication, namely

"Acute lymphocytic leukemia (ALL) as second-line treatment in adults and children"

comprising also a dose recommendation for this indication(s) in sec. 4.2

Furthermore, in section 4.4 an additional warning concerning a higher susceptibility of children to anthracycline-induced cardiotoxicity is proposed.

Finally, based on PK trials submitted, also an amendment of the description of idarubicin PK after i.v. and oral administration in children is proposed for sec. 5.2. of the SmPC.

Similar changes are proposed for the PL (sec. 1 and 2) except information limited to the SmPC only (such as information on PK).

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

1. An annex including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product.

Update concerning the responses to the LoQ as of October 3rd, 2011:

With the responses as of October 3rd 2011 the MAH is proposing the following, revised (paediatric) indications for the SmPC (sec. 4.1):

Idarubicin is indicated for first-line treatment of children with acute myeloid leukemia (AML) or for remission induction in paediatric patients with relapsed or refractory AML.

Idarubicin is indicated as second-line treatment in children with Acute lymphocytic leukemia (ALL)

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Not applicable

IV.2 Non-clinical aspects

1. Introduction

No non clinical trials have been submitted.

2. Non clinical study(ies)

NON CLINICAL STUDY NUMBER and TITLE

N/A

3. Discussion on non clinical aspects

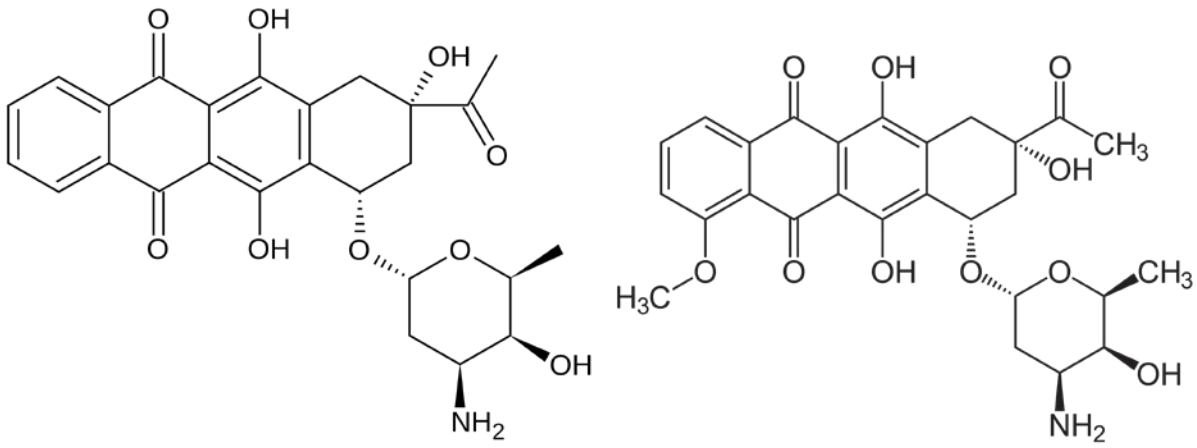
N/A

IV.3 Clinical aspects

1. Introduction

Idarubicin (4-demethoxydaunorubicin) is a daunorubicin analogue.

Figure 1: Idarubicin (4-demethoxydaunorubicin) vs. Daunorubicin



The absence of a methoxyl group at position 4 of idarubicin's anthracycline structure (see left hand side of

Figure 1) results in an increased lipophilicity and rate of cellular uptake compared with daunorubicin.

Accordingly, idarubicin can be administered orally and it is more effective on a molecular basis. In terms of “equi-effective” dosage the latter is correct since the therapeutic dosages of idarubicin are considerably smaller than therapeutic dosages of daunorubicin. For example, the recommended dose for idarubicin in (adult) AML/ANLL in combination with cytarabin is 3x12 mg/m^2 (or 5x8 mg/m^2) whereas the recommended dosage for single dose daunorubicin (in combination with cytarabin in adult AML) for a 3 days cycle is 45 mg/m^2, thus, idarubicin dose by a factor or 3 to 4 smaller even in terms of molecular weight as the latter is comparable for both substances. A factor of 4 (1 mg idarubicin can replace 4 mg daunorubicin) has been proposed and investigated in children with previously untreated AML - doi: 10.1200/JCO.2004.04.016:

“CONCLUSION: In CCG-2941, excessive toxicity and withdrawals outweighed potential benefits of early response with IDA.”.

Bioavailability of orally administered idarubicin varies widely between patients and studies, although a mean of about 30% was generally observed. Important to recall is that idarubicin is rapidly converted by the liver to its only detected metabolite, idarubicinol, and higher concentrations of idarubicinol are produced following oral rather than intravenous dosing, probably due to first pass metabolism in the liver. In vitro, idarubicinol (4-demethoxy-daunorubicinol) demonstrated similar activity to idarubicin.

Daunorubicin is widely used in adult and childhood acute leukaemias. Although doxorubicin is the more favoured anthracycline used in ALL whereas in AML/ANLL daunorubicin is favoured (mostly for historical reasons). Accordingly, daunorubicin is licensed (at least in the RMS for this paediatric/art. 45 procedure) for both (adult and childhood) ALL and AML. In contrast to the MA status of daunorubicin, idarubicin itself is granted a MA in the RMS only for adult AML although it may have, theoretically, similar or widely overlapping indications with the elder substance daunorubicin.
Idarubicin has also some activity in (adult) solid tumours but in the context of an article 45 procedure considerations concerning this property can be left out.

From the assessor’s point of view, therefore, the question of the effectiveness and equi-toxicity of idarubicin, compared to daunorubicin, in **paediatric AML** would be the clue for this procedure. Therefore it is both significant and remarkable that the MAH discusses in the clinical overview primarily (second line treatment) of ALL (in adults and?) in children but not AML in children.

The MAH submitted 9 report(s) for:

- **Protocol No. 799-ONC-9041-184**

  Sub-center report on randomized, open, multi-center, parallel, controlled clinical study comparing the efficacy and safety of idarubicin produced in China to imported idarubicin.

- **Protocol No. 95-OIDV-090**

  Multinational, Multi-Center, Randomized, Active-Controlled, Open-Label Study for the Treatment of Acute Myeloblastic Leukemia in Treatment-Naive Children

- **Protocol No. IMI 30/762i**

  A phase III trial comparing daunorubicin or idarubicin combined with cytosine arabinoside in acute myelogenous leukemia (AML)

- **Protocol No. IMI 30/615i / Study No. 083F03**

  4-Demethoxydaunorubicin (4DMDR) in Children with Advanced Malignancies: Phase I Study of Oral 4 DMDR and the Clinical Pharmacology of Oral Administration

- **Protocol No. IMI 30/794i / Study No. ZA 87602**

  Combination chemotherapy with arabinosylcytosine (ARA-C), 4-demethoxydaunorubicin (4-DMDR) (idarubicin) and VP-16 in patients with acute non-lymphocytic leukemia

- **Protocol No. IMI 30/795i / Study No. DD 84601**

A Phase II Study of Oral Idarubicin in Children with Acute Leukemias: Evaluation of Toxicity and Efficacy

- **Protocol No. IMI 30/796i / Study No. ZA 84601**

Oral idarubicin in combination with cytosine-arabinoside in previously untreated patients with acute non-lymphocytic leukaemia

- **Protocol No. IMI 30/799941i / Study No. 073023**

Determination of dose of idarubicin in combination with VPL for remission reinduction in ALL after 1st marrow relapse; alternative induction while awaiting results in IDR patients – VPL in combination with daunomycin: a groupwide feasibility study

- **Progress Report No. IMI 30/746i**

Progress Report to Adria Laboratories on Pediatric Idarubicin Studies

2. Clinical study(ies)

I. Protocol No. 95-OIDV-090

Protocol Title: Multinational, Multi-Center, Randomized, Active-Controlled, Open-Label Study for the Treatment of Acute Myeloblastic Leukemia in Treatment-Naive Children

Summary (as provided by the clinical overview): The primary objective of this study was to establish the efficacy and toxicity of an intensification phase with idarubicin (IDA) + high doses of cytosine arabinoside (Ara-C) versus high doses of Ara-C plus etoposide as second drug of the schedule in terms of the duration of complete response and survival, and comparison of adverse events (AEs) in both arms. Treatment-naïve subjects under 16 years of age with a diagnosis of AML were included in this Phase 3 study. Thirty-two subjects were enrolled. Of these, 27 subjects were at standard risk and 4 subjects at high risk; data for 1 subject was not available. Treatment with idarubicin was well tolerated. Response to induction was complete for the majority of subjects (27 subjects, 84.4%). At the end of treatment, 25 subjects (78.1%) had no evidence of the disease. There were no deaths reported for this study and no subjects discontinued due to an AE. One SAE (cerebral ischemia) occurred in one subject, a 2 year old male, 13 days after stopping treatment with idarubicin. The event was considered not related to the drug under study by the investigator.

Assessor's comment:

For this trial a kind of a 3 pages long abstract/summary (in addition of the description by the MAH given above) has been submitted but not the final report and/or the study protocol. Therefore it is difficult (if not impossible) to determine the relevance of this trial for a paediatric population as not even minimal data (such as age range of the patients investigated) have been presented.
If presented adequately, the trial could potentially allow to grant an intensification indication to idarubicin in the context of first line treatment of AML in childhood. However, the information

offered by the MAH on this trial is very limited and the MAH is not proposing and intensification indication in AML (of childhood).

II. Protocol No. 799-ONC-9041-184

Protocol Title: Sub-center report on randomized, open, multi-center, parallel, controlled clinical study comparing the efficacy and safety of idarubicin produced in China to imported idarubicin.

Summary (as provided by the clinical overview): The primary objective of this study was to evaluate the efficacy and safety of domestic and imported idarubicin (IDA) injections in treating AML and ALL. This study involved a total of 66 leukemia patients, ages 14 through 67 (with unknown number of paediatric patients), randomly assigned to two groups according to AML and ALL status:
Group A (Domestic IDA) and Group B (Imported IDA). Sixty (60) of these patients completed the treatment and were included in the efficacy evaluation. AML patients used an idarubicin and cytarabine (IA) combination regimen. ALL patients used an idarubicin, Vindesine, cyclophosphamide, and prednisone combination regimen (VICP). Treatment continued for a maximum of 2 courses. The results of the study showed that domestic and imported idarubicin combination chemotherapies have significant and equal efficacy in treating acute leukemia. For the domestic and imported idarubicin groups, overall efficacy at the end of the trial was 89.65% and 93.55%, respectively. Most patients who achieved complete remission did so by the end of the first course. Among the 43 AML patients, there were no obvious statistical differences in efficacy between the two groups: 86.37% (domestic group) vs. 95.24% (imported group). Similar results were reported among the 17 ALL patients in which total efficacy rates at the end of trial were 100% for both groups. The median time to remission of clinical signs and symptoms among patients who achieved remission was 29.5 days for the domestic group and 24.0 days for the imported group. There was no significant difference in total cases and incidence of adverse events between the domestic and imported groups. As with other anthracycline drugs used in chemotherapy, the most common adverse reactions were related to blood, the gastrointestinal system, and hair presenting as myelosuppression, gastrointestinal reactions (nausea, vomiting, oral mucosal ulcers), and reversible hair loss.

Assessor's comment:

Although the study report submitted is slightly more informative than the 3 pages submitted for study 95-OIDV-090, the relevance of trial 799-ONC-9041-184 for a paediatric population cannot be determined. Already the MAH/clinical expert states that the number of paediatric patients involved is unknown.

From the assessor point of view the trial is also too small to determine non-inferiority, or equivalence of domestic vs. imported idarubicin. Rather, the trial was small enough not to reveal any statistically significant difference of both products.

III. Protocol No. IMI 30/762i

Protocol Title: A phase III trial comparing daunorubicin or idarubicin combined with cytosine arabinoside in acute myelogenous leukemia (AML)

Summary (as provided by the clinical overview): Newly diagnosed adult (> 15 years; includes one 17 yo paediatric patient) AML patients were treated with Cytosine arabinoside (CA), 100 mg/m^2/day by continuous infusion for 7 days after being randomized to receive either

daunorubicin, 45 mg/m^2 or idarubicin, 12 mg/m^2/day by slow IV infusion the first 3 days. A 2nd course was given if the marrow performed 7 days after completion of therapy showed persistent leukemia. If the marrow was hypocellular, examination was repeated every 7 days until a response could be determined. Those failing to achieve complete remission (CR) after 2 courses were taken off study. Of the 157 patients registered on the study, 73 were randomized to receive idarubicin, and 84 to daunorubicin. There were no differences in distribution by sex, age, performance status, presence of infection, bleeding, median WBC or platelet count. To date, data are available on 85 patients. Of patients given idarubicin, 29 of 39 (74%) and of those given daunorubicin, 26 of 46 (57%) achieved CR (p = 0.086). A second induction course was required in 7 patients given idarubicin and 6 given daunorubicin. There was no statistically significant difference in the frequency or severity of cardiac, hepatic, renal, pulmonary, gastrointestinal, or cutaneous toxicities. The data suggest that idarubicin is an effective antileukemic agent when combined with CA.

Assessor's comment:

The report as actually submitted seems to be an interim report of a (pivotal) trial in (previously untreated) adult AML patients for which the final results have been published in 1992 - J Clin Oncol 10: 1103-11, 1992, see http://jco.ascopubs.org/content/10/7/1103.full.pdf . It may represent one of several trials submitted for the national MA granted for adult AML in the RMS DE around 1990. In line with those trials this trial demonstrated a higher frequency of CR after remission induction with idarubicin (+AraC) compared to daunorubicin (+AraC).
It is acknowledged that in the interim report submitted a single patient was younger than 18 years. Otherwise the relevance of this trial for AML in children seems to be minor.

IV. Protocol No. IMI 30/615i / Study No. 083F03
Protocol Title: 4-Demethoxydaunorubicin (4DMDR) in Children with Advanced Malignancies: Phase I Study or Oral 4 DMDR and the Clinical Pharmacology of Oral Administration

Summary (as provided by the clinical overview): This study was designed to establish an oral dose of 4-demethoxydaunorubicin (4DMDR) that reliably produces biological effects in children with advanced cancer, and to characterize these effects. Patients ≤ 18 years of age with histological proof of malignancy who were not candidates for treatment with regimens of established efficacy were eligible. Patients must have been off all previous therapy for 4 weeks prior to entry and/or have recovered from the toxic effects of any prior therapy. Therapy consisted of daily 4 DMDR administered orally on 3 consecutive days according to the following dose escalation schedule: Leukemia patients (20 mg/m^2/day x 3 days; 30 mg/m^2/day x 3; 40 mg/m^2/day x 3 days); Solid tumor patients (10 mg/m^2/day x 3 days; 20 mg/m^2/day x 3 days; 30 mg/m^2/day x 3 days. A course could be repeated every 21 days. Three patients were to be treated at each dose level until a dose was achieved which produced objective toxicity. Once this dose level was reached, escalation was to continue by smaller increments (15-20%) until the MTD was established. Twenty-nine (29) were entered and included 11 patients with ALL and 4 patients with AML/ANLL (ages .75 to 16 years). Of the patients with solid tumors, 7 had progressive disease. Seven leukemia patients had progressive disease. One patient with ALL achieved a complete response lasting 112 days. The remission occurred after 2 induction courses of 90 mg/m^2 and 120 mg/m^2 of idarubicin, respectively. Subsequent patients were treated with doses of 90-150 mg/m^2 with no further responses. In patients with leukemia, mucositis and diarrhea were dose-limiting at doses higher than 90 mg/m^2/course. In patients with solid tumors, the MDT was less definite but will probably be considered to be 60-70 mg/m^2/course. At this latter dose, the only severe toxicity reported was myelosuppression. Even at the highest doses used the antileukemic efficacy of the drug was less than that observed in a

similar patient population treated with intravenously administered idarubicin. No responses were seen in patients with a variety of solid tumors. However, the efficacy of the drug is difficult to evaluate in a patient population that had received extensive prior therapy.

Assessor's comment:

This trial actually investigated 15 paediatric patients with acute leukemias (4 with AML/ANLL and 11 with ALL). However, patients were heavily pretreated.

Taken into account the overall conclusion of the investigators - "The investigator concluded that in patients with leukemia, mucositis and diarrhea are doselimiting at doses higher than 90 mg/m2/course. In patients with solid tumors, the MDT is less definite but will probably be considered to be 60-70 mg/m2/course. At this latter dose, the only severe toxicity reported was myelosuppression. Even at the highest doses used the antileukemic efficacy of the drug was less than that observed in a similar patient population treated with intravenously administered idarubicin. No responses were seen in patients with a variety of solid tumors. However, the efficacy of the drug is difficult to evaluate in a patient population that had received extensive prior therapy." - one may conclude that oral idarubicin is no optimal option in the second or last line treatment of acute leukemias in childhood. However, since the trial was not randomized, the stated smaller antileukemic effect of oral vs. i.v. idarubicin in "comparable populations" is difficult to follow.
At least a MTD of oral idarubicin in leukemias (30 mg/m^2/day in courses of 3 consecutive days) and solid tumours have been established. Furthermore, the trial shows that oral administration of the capsules is feasible in a last line paediatric leukaemia population.

Finally, the trial has generated (paediatric) PK data for idarubicin and idarubicinol after oral administration of idarubicin.

V. Protocol No. IMI 30/794i / Study No. ZA 87602

Protocol Title: Combination chemotherapy with arabinosylcytosine (ARA-C), 4-demethoxydaunorubicin (4-DMDR) (idarubicin) and VP-16 in patients with acute non-lymphocytic leukemia

Summary (as provided by the clinical overview): This was an uncontrolled open label phase II study, designed to evaluate the efficacy of the combination of oral idarubicin, intravenous (IV) arabinosylcytosine (Ara-C) and etoposide (VP16), in the induction of complete remission in patients with acute myeloid leukemia. From October 1986 to April 1988, 20 patients entered the study; the median age was 42 years (range 4-72), with 4 paediatric (age < 14 years) patients, 12 adult (age 27 to 58), and 4 elderly (over 60 years). Patients received oral idarubicin 20 mg/m^2/day for three consecutive days, in combination with IV Ara-C 25 mg/m^2 as a loading dose, followed by a continuous infusion of 200 mg/m^2/day on days 1-5, and IV VP16 100 mg/m^2/day on days 1-5. Duration of administration of drugs was shortened in patients over 65 years old. One to two induction cycles were to be given, followed, in responding patients, by a consolidation course and a maintenance therapy with the same drugs used in induction. Peripheral blood counts, blood chemistry, bone marrow aspirate, and cardiac evaluation were performed before and during the study.
Five out of the 20 evaluable patients achieved a complete remission (25%), 3 after the first, and 2 after the second induction cycle. Median time to CR was 47 days (range 30-104). Response rates by prior treatment were 17.6 and 66.7%, respectively, in untreated and pretreated patients. Fifteen patients were considered therapeutic failures. Of these, nine died during the induction phase of therapy, all in severe myelosuppression. Median survival duration was 25.5 days

(range 13-663). The main toxicity was hematologic, being median WBC nadirs less than 1000/mm^3 during the two induction courses, and paralleled by a median neutrophil nadir of 0; the median platelet nadir was 9 and 10.5 x 10^3/mm^3 in 1st and 2nd course, respectively. Infectious episodes complicated 60% of first, and 100% of second induction courses. Regarding non-hematologic toxicity, the most frequent complaints were nausea, vomiting and mucositis. No cardiac or neurologic toxicities were reported during the whole treatment. Only one grade 3 episode (diarrhea) was recorded during consolidation. In conclusion, the association of oral idarubicin + Ara-C + VP16 is undoubtedly myelosuppressive and rather well tolerated as far as non hematological toxicity is concerned; the poor results obtained in the present study could be ascribed mainly to the severe hematological toxicity observed, and to the subsequent high rate of induction deaths.

Assessor's comment:

The overall conclusion of the investigators ("…the poor results obtained in the present study could be ascribed mainly … to the subsequent high rate of induction deaths") must be put into relation to a preceding trial of the same investigators. In the study report it is stated that "an earlier study was performed by the same authors in 24 ANLL patients treated with oral idarubicin 20 mg/m^2 /day for 3 days and Ara-C IV 25 mg/m^2 push + 100 mg/m^2/day for 5 days (and without VP-16), obtaining 13 CR, or a 54.2% CR rate. The present study was performed to optimize the therapeutic regimen, …" (and obviously failed to confirm that intensification in terms of higher Ara-C dose and additional etoposid does optimize therapy). As such this trial would indicate that oral administration of idarubicin is possible also in paediatric AML patients. The unfavourable result of this trial, however, and the result of the earlier trial do not suggest that oral idarubicin (in the investigated combination) is an optimal (first-line) treatment of (paediatric) patients with previously untreated AML. 17 of the 20 patients investigated in this trial were previously untreated patients with AML.

VI. Protocol No. IMI 30/795i / Study No. DD 84601

Protocol Title: A Phase II Study of Oral Idarubicin in Children with Acute Leukemias: Evaluation of Toxicity and Efficacy

Summary (as provided by the clinical overview): This was an open label, uncontrolled, multicentre phase II study designed to evaluate the efficacy and safety profile of oral idarubicin, at a dose of 14-30 mg/m^2/day on days 1-3 as induction treatment in children with relapsed or refractory acute lymphoblastic (ALL) or acute myeloid (AML) leukemia.
Twenty patients – 11 males, median age 13 years, 18 with ALL and 2 with AML – were enrolled. One (16 pts) to three induction cycles with the study drug, combined with other agents in 6 first and one second course, were administered. Hematological and biochemical profile, together with clinical condition and cardiac function, were assessed prior to and during study.
A complete remission (CR) was achieved in 4 cases (20%, 95% CI: 5.73-43.66), all with ALL (3 in second relapse, 1 refractory). Three children achieved a PR with the first course and were withdrawn for unknown reasons.
Myelosuppression (as white blood cell counts < 1000/mm^3) was achieved in 70.6% of the cases receiving the first cycle, and was of relatively short duration (median 6 days). Infectious episodes occurred in 7/29 (24%) courses: 4 episodes were in the first cycle (20%). Main non hematological toxicity was gastrointestinal (mostly nausea and vomiting); a grade 3 severity was attained in one patient. Two children experienced grade $\leq$ 2 cardiac problems. In conclusion, oral idarubicin administered to very poor prognosis children with acute leukemia at doses inducing limited myelosuppression (and ranging from 35 to 75% of the maximally tolerated one), showed an adequate antileukemic effect coupled with a good tolerability profile. However,

further studies are needed to evaluate the real yield of the compound in this category of patients, when given by oral route at adequate doses, in an intensive approach.

Assessor's comment:

The trial indicates in the feasibility of an oral idarubicin second line treatment of children with ALL (and AML/ANLL). In addition, this phase II trial indicates in some antileukaemic effects of oral idarubince in relapsing or refractory paediatric ALL (but not AML) patients while toxicity of the schedule investigated seems to be acceptable.
In agreement with the authors, however, the assessor is of the opinion that further studies are needed and that this phase II trial cannot be the (single) source for granting a MA in 'acute lymphocytic leukemia (ALL) as second-line treatment in ~~adults and~~ children', as proposed by the MAH.

VII. Protocol No. IMI 30/796i / Study No. ZA 84601
Protocol Title: Oral idarubicin in combination with cytosine-arabinoside in previously untreated patients with acute non-lymphocytic leukemia

Summary (as provided by the clinical overview): This was an uncontrolled open label phase II study, designed to evaluate the efficacy of the combination of oral idarubicin and arabinosylcytosine (Ara-C) in the induction of complete remission in untreated patients with acute non-lymphocytic leukemia. There were 24 eligible subjects, 11 males and 13 females with a median age of 43.5 years (range 11-72). Of the 24 eligible subjects, 2 were paediatric (< 16 years) and 5 were > 60 years. Patients received oral idarubicin 20 mg/m^2/day for three consecutive days, in combination with Ara-C IV 25 mg/m^2 as a loading dose, followed by a continuous infusion of 100 mg/m^2/day on days 1-5. Peripheral blood counts, blood chemistry, bone marrow aspirate and cardiac evaluation were performed before and during the study. Thirteen out of 24 evaluable patients achieved a complete remission (54.2%), 9 after the first, and 4 after the second induction cycle. Median time to CR was 35 days (range 22-112); median duration of CR was 149 days (range 46-1125). Eleven patients were considered therapeutic failures. Seven patients, one of whom in CR, died during the induction phase of therapy. Median survival duration was 109.5 days (range 13-1153).
The main toxicity was hematologic, being median WBC nadirs less than 1000/mm^3 during the two induction courses, and paralleled by a median neutrophil nadir of 0; the median platelet nadir was 9.5 and 10 x 10^3/mm^3 in 1st and 2nd course, respectively. Regarding non-hematologic toxicity, the most frequent complaints were nausea, vomiting, and mucositis. In induction, one patient had grade 3 cardiotoxicity, and three grade 3 neurotoxicity. No grade 4 toxicity was recorded. In consolidation, no grade 3 toxicity and no cardiotoxicity were recorded; one patient experienced CNS grade 1 side effects. In conclusion, the present study evidenced that the combination of idarubicin and Ara-C has significant activity and limited toxicity in previously untreated patients with acute non-lymphocytic leukemia.

Assessor's comment:

This trail is the trial preceding the already discussed trial "V. Protocol No. IMI 30/794i / Study No. ZA 87602" above.

Insofar the assessor's comment made on the subsequent trial ZA 87602 apply also on the preceding trial (oral administration of idarubicin is possible also in paediatric AML patients.) albeit the number of 2 paediatric patients investigated is rather small. It may be mentioned that the CR rate in the first trial was considerably higher than an the subsequent trying to improve the result of the first (54.2% vs. 20%). But also the 54.2% CR frequency observed for an oral

idarubicin schedule does not imply that the oral is actually the optimal route of idarubicin administration as already discussed in context with trial IMI 30/794i / Study No. ZA 87602 comparing this result with the findings of the Study No. 083F03
The assessor, already involved in the original MAA for Zavedos for the German market, would like to add that the (national) labelling of Zavedos (i.v..) and Zavedos oral also reflects the fact that oral idarubicin treatment is suboptimal compared to i.v. administration at least in the first line treatment of adult AML patients. A potential cause may be the higher variability of idarubicin and idarubicinol plasma levels after oral administration compared to i.v. administration – and the clear concentration-effect relationship for the mylosuppressive effects of idarubicin/idarubicinol.

VIII. Protocol No. IMI 30/799941i / Study No. 073023

Protocol Title: Determination of dose of idarubicin in combination with VPL for remission reinduction in ALL after 1st marrow relapse; alternative induction while awaiting results in IDR patients – VPL in combination with daunomycin: a groupwide feasibility study

Summary (as provided by the clinical overview): This was an unblinded, uncontrolled, double-arm, multicenter study designed to determine the maximum tolerated dose (MTD) of IV idarubicin when given in combination with vincristine, prednisone, and L-asparaginase. This study was conducted by participants of the Childrens Cancer Study Group (CCSG). Ninety-one patients (ages 1-17 years) experiencing relapse of ALL were enrolled. The results are reported in the publication of this study (Feig et al, 1992).

Summary (of the Feig publication as of the clinical overview):

Feig et al (1992) - doi: 10.1002/mpo.2950200207 - reported the results from an escalating dose trial of idaruabicin conducted by the Children's Cancer Study Group. Idarubicin was administered weekly for 3 doses in a multidrug regimen to reinduce remission of childhood ALL at first bone marrow relapse. The maximum tolerated dose (MTD) of idarubicin was determined to be 12.5 mg/m^2/dose. Twelve of 16 (75%) evaluable patients treated at a dose of 10 mg/m^2 or 12.5 mg/m^2 entered a second complete remission, compared to 41 of 69 evaluable patients (59%) treated in a comparable way with daunorubicin 30 mg/m^2. Severe and prolonged myelosuppression was observed in both groups, although the frequency of bacterial sepsis and duration of hospitalization were greater among patients treated with idarubicin. No additional toxicity was observed with idarubicin at these doses.

Published abstract:

An escalating-dose trial of idarubicin, used weekly for 3 doses in combination with vincristine, prednisone, and L-asparaginase (VPLI), to reinduce remission of childhood ALL at first bone marrow relapse was conducted by the Childrens Cancer Study Group (CCSG). The maximum tolerated dose (MTD) of idarubicin, used in the manner, was determined to be 12.5 mg/m^2/dose. Twelve of 16 (75%) evaluable patients in first marrow relapse of ALL treated at a dose of 10 or 12.5 mg/m^2 entered a second complete remission, compared to 41 of 69 evaluable patients (59%) treated in a comparable way with daunorubicin (30 mg/m^2) (VPLD). Prolonged myelosuppression was observed in both groups, but the frequency of documented bacterial sepsis and the duration of required hospitalization were greater among patients treated with idarubicin. No additional toxicity, specifically attributable to idarubicin, was observed at these doses (Medical and Pediatric Oncology 20: 124–29, 1992; see http://onlinelibrary.wiley.com/doi/10.1002/mpo.2950200207/abstract).

Assessor's comment:

This is a comparative (but not randomized) phase I to II dose finding trial in the indication proposed (second line treatment of ALL in children). The slightly higher CR as well as the higher (myelo-) toxicity compared to the daunorubicin arm indicate that idarubicin may be a valuable substance in second line treatment of first (bone marrow) relapse in children with ALL. In accordance with the authors of this trial/publication one can conclude that "further studies may be warranted to substantiate the maximum tolerated dose of idarubicin in this therapeutic regimen." Since the trial has been conducted in 1986/87, and published in 1992 the question may be allowed in 2011 where those, and confirmatory, trials are.

IX. Progress Report No. IMI 30/746i

Report Title: Progress Report to Adria Laboratories on Pediatric Idarubicin Studies

S**ummary (as provided by the clinical overview):** This report provides a summary of **Study 81-85** [4-Demethoxydaunorubicin (4-DMDR) in children with advanced cancer (IV)] and **Study 83-31** [4-Demethoxydaunorubicin (4-DMDR) in children with advanced malignancies: phase I study of oral 4-DMDR and the clinical pharmacology of oral administration]. Patient age ranged from 0 to 19 years. Idarubicin was given IV to 46 children (28 leukemia, 18 solid tumor) and orally to 20 children (13 leukemia, 7 solid tumor) with advanced malignancies. The drug was given in three daily doses every 2-3 weeks. Myelosuppression was the dose-limiting toxicity; nadir usually occurred on day 14 with recovery by day 21-28. Vomiting and diarrhea were common after oral doses. No cardiac toxicity has been seen after oral doses. Four of the 41 patients receiving IV courses developed congestive heart failure, associated with infection and bleeding. For IV idarubicin, the MTD was determined to be 15 mg/m^2 (solid tumor patients) and 30 mg/m^2 (leukemia patients). For the oral formulation, the MTD was 60 mg/m^2 (solid tumor patients) and 120 mg/m^2 (leukemia patients). Intravenous idarubicin produced remissions in about 50% of children with acute lymphoblastic leukemia. Only two of seven children with acute nonlymphoblastic leukemia had brief responses. Orally, one of ten children with acute lymphoblastic leukemia achieved complete remission.

Assessor's comment:

Concerning this 10 pages long "progress report" it is difficult to depict more information/details than given in the summary above. At least the patients with leukaemias appear to be pretreated children (age range given as 1-19 years) since the lower limit of the range of 'Prior Anthracycline Median (mg/m^2)' is larger than zero in leukaemia patients.
No final report (and protocol) for trials 81-85 and 83-31 have been submitted with the dossier assessed here.

Clinical Studies in Published Literature:

In addition to these 9 either partially (investigators initiated) or fully MAH sponsored trials discussed above, to which the MAH has (full) access, two series of publications are discussed in the clinical overview as follows:

A. Idarubicin as Second-Line Therapy in Acute Lymphocytic Leukemia (ALL) in Children – clinical studies supporting this indication in the CDS

Under this heading overall 3 published trials, being part of the companies Core Data Sheet (CDS), and submitted within the dossier for this procedure, are described as follows **(Summaries as provided by the clinical overview)**:

A.1: Tan et al (1987) - Cancer Res 47: 2990-95, 1987; see also http://cancerres.aacrjournals.org/content/47/11/2990.full.pdf+html reporting the results from a Phase I and clinical pharmacological study of idarubicin in children with advancer cancer found that idarubicin was effective in achieving bone marrow remissions in children with refractory or relapsed acute leukemia. Escalating doses of 10 to 40 mg/m^2/course were administered to children (ages ranging from 1-19 years) in 3 equal fractions x 3 consecutive days at 14- to 21-day intervals. Six of 15 evaluable patients (40%) with ALL who received $\geq$ 30 mg/m^2 course of idarubicin achieved a remission compared with 2 of 8 evaluable patients (25%) with ANLL. The maximum tolerated dose in solid tumor patients was 15 mg/m^2/course in 3 divided doses. Leukemia patients tolerated the 30 mg/m^2/course. Dose limiting toxicities for short-term administration were myelosuppression and mucositis. Other observed toxicities were nausea, vomiting, and elevation of liver enzymes and bilirubin. There were patients with mild cardiac function changes without clinical symptoms. Four patients presented with CHF. Peak toxicity occurred 2 weeks after start of drug therapy with median recovery by day 24.

Assessor's comment:

The clinical assessor is endorsing the overall conclusion of the authors which reads:

"While the cardiotoxic dose still must be delineated, the complete remissions achieved in multiple relapsed patients with acute lymphoblastic leukemia indicate promising activity in at least that disease."

The MTD (for leukaemias in general) determined was 10 mg/m^2 x 3 days (30mg/m^2/course):

"Patients with leukemia tolerated 30 mg/m^2/course."

A.2: Feig et al (1992) - doi: 10.1002/mpo.2950200207 see ***VIII. Protocol No. IMI 30/799941i / Study No. 073023*** above, subheading 'published abstract'.

Assessor's comment:

It may be recalled that this trial determined a single dose MTD of 12.5 mg/m^2 (37.5 mg/m^2/course) idarubicin (as part of a combination [VPLI] regimen) in ALL which is approximately the same (actually slightly higher) as determined by A.1: Tan et al (1987) above for an idarubicin monotherapy regimen. It may, however, be reiterated that this trial/publication did conclude that "further studies may be warranted to substantiate the maximum tolerated dose of idarubicin in this therapeutic regimen."

Feig et al (1996) - doi: 10.1002/(SICI)1096-911X(199612)27:6<505::AID-MPO1>3.0.CO;2-P; see also http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1096-911X(199612)27:6%3C505::AID-MPO1%3E3.0.CO;2-P/pdf reported the results from Children's Cancer Group study 1884 of multidrug treatment of first bone marrow relapse of childhood ALL. Compared to DNR (45 mg/m^2/week x 3), IDA 12.5 mg/m^2/week x 3) was associated with prolonged myelosuppression and more frequent serious infections. Halfway through the study, the dose of IDA was reduced to 10 mg/m^2. Overall, second remission was achieved in 71% of patients. Reinduction rate was similar for IDA and DNR, 73% and 69%, respectively. Reasons for induction failure differed; 0 of 15, 1 of 5, and 5 of 7 reinduction failures were due to infection for DNR, IDA (10 mg/m^2), and IDA (12.5 mg/m^2), respectively. Two-year event-free survival (EFS) was better among patients who received IDA 12.5 mg/m^2 (27 $\pm$ 18%) compared to DNR (10 $\pm$ 8%, *P* = 0.05) and IDA 10

mg/m^2 (6 ± 12%, *P* = 0.02). However, after 3 years of follow-up, late events in the high-dose IDA group resulted in a similar EFS to the lower-dose IDA and DNR groups.

Assessor's comment:

A randomized trial like this could, in principle, be the basis for granting the indication "Acute lymphocytic leukemia (ALL) as second-line treatment ~~in adults and~~ children" within a variation type II for an otherwise well established substance, an indication currently proposed by the MAH for this work sharing procedure (in order to vary authorized SPCs in the MS later).
The problem is here, however, not primarily the adult indication proposed as therapeutic principles in adult ALL follow principles worked out and set up in the (rather successful) treatment of the more frequent childhood ALL.

Rather, the assessor sees three more relevant problems:

*1. In the current, relevant German (and US) treatment guidelines induction treatment is risk adapted, i.e. the higher relapse risk is the more intensive (first) induction treatment is recommended. In some (relevant) US guidelines it is even recommended **not** to use first line anthracyclines for remission induction in low risk ALL patients. In German guidelines, the one and only anthracycline recommended explicitly for first remission induction is daunorubicin. Both in the US and in Germany, general recommendation is to use – in principle – for means of second remission induction (after first BM relapse) the same regimens recommended for high risk first induction. Thus, a differentiation of first and second line therapy (in the sense of second induction after first relapse) of ALL is rather meaningless for the SmPC of most if not all medicinal products. Rather, the question to solve for any SmPC is whether a specific substance/product is to be recommended for induction regimens in low and/or high risk patients..*
2. Idarubicin is not (explicitly) recommended in ALL following the relevant therapeutic guideline of the RMS- http://www.awmf.org/uploads/tx_szleitlinien/025-014.pdf (= AWMF: Akute lymphoblastische (ALL) und akute myeloische (AML) Leukämie im Kindesalter). Thus, the trial Feig et al. (1996) had obviously no amenable impact on the relevant therapeutic guidelines (including US) consulted by clinical assessor, i.e. this trial did not change clinical practice on both sides of the Atlantic.
3. Following the results of the trial published by Feig et al. (1996) both IDA 10 and 12.5 mg/m^2/week x3) appear to be more toxic than (standard dose) daunorubicin. IDA 10 does not offer an additional benefit so that the benefit risk assessment of the lower IDA dose is negative. IDA 12.5 is considerably more toxic than standard daunorubicin (more precise: too toxic already affecting the course of the trial) but offers no long term benefit. In effect, this trial does not justify to replace standard dose daunorubicin by 10 or 12.5 mg/m^2 for 3 days in a week idarubicin in a second line induction regimen.

In summary, the clinical assessor is objecting to add (in the RMS - eventually 'to modify' in the SmPCs of the CMS involved) the indication "Acute lymphocytic leukemia (ALL) as second-line treatment in adults and children" as proposed by the MAH provided that this publication is the one and only source of confirmatory evidence for idarubicin used in this indication.

B. Other Relevant Studies

Under this heading overall 9 published trials of idarubicin in (childhood) ALL (and AML) are reviewed by the MAH. Their common feature is that they are not part of the company's CDS, and have not been submitted with the dossier for this procedure. The latter is not very relevant

for the assessment but the overall efficacy conclusion directly following the literature review. This reads:

> "The MAH identified 9 relevant studies/reports to support the paediatric assessment. The data on file for paediatric patients is limited, and includes several studies of the oral formulation administered in children with ANLL/AML for which there no current approved indication. The data in the published reports support the efficacy of idarubicin in paediatric patients with ALL, confirming that the use of idarubicin is well established in current paediatric clinical practice. Established dosing regimens generally range from 10 to 12 mg/m^2/day for 3 days."

The **literature review** by the MAH is offered here below. The assessor's comment that will follow this review will discuss the efficacy conclusion of the MAH.

> **"Pui et al (1988)** reported the results from a phase I clinical trial of orally administered idarubicin with pharmacokinetic and *in vitro* drug sensitivity testing in children with refractory leukemia. Fifteen (15) children (ages 5-17 years) with acute leukemia (9 ALL; 6 ANLL) in relapse were treated with idarubicin orally for 3 consecutive days in dosages ranging from 30 to 50 mg/m^2 at 19-21 day intervals. Gastrointestinal complications, including nausea, vomiting, abdominal pain, diarrhea and stomatitis were the major dose limiting toxicities affecting the majority of patients at all dose levels. Two patients who had received total-body irradiation for bone marrow transplantation developed life-threatening gastrointestinal toxicity suggestive of a radiation "recall" phenomenon. Echocardiographic evidence of depressed cardiac function, without clinical signs or symptoms, was noted in 6 of 11 patients, although changes were judged to be significant in only one child. The maximum tolerated oral dose of idarubicin was 40 mg/m^2 per day. The PK results from this study are discussed in Section **Fehler! Verweisquelle konnte nicht gefunden werden.**. Among the five patients with acute non-lymphoblastic leukemia whose cells were tested for drug sensitivity in vitro, the idarubicin concentration resulting in 50% inhibition (IC_{50}) of cluster and colony formation ranged from 1.6 x 10^{-10} M to 5 x 10^{-7} M. There was no obvious relationship between the IC_{50} for idarubicin and that for epirubicin or daunorubicin. Oral idarubicin produced definite antileukemic effects, clearing blast cells from the circulation in 13 of the 14 evaluable patients.
>
> **Giona et al (1990)** reporting the results of an Italian cooperative trial using an induction regimen of IDA plus high-dose Ara-C for refractory or relapsed ALL, found an overall 59% CR rate, with 68% CR rate in (21/31) children and 54% in (31/57) adults. The CR rate was significantly affected by WBC count at the beginning of treatment and by the duration of first CR of the patients treated in the first relapse. All of the patients experienced profound myelosuppression. Nausea and vomiting occurred in 45 patients, 35 patients developed stomatitis which was severe in only one case, 20 patients had diarrhea, and 14 patients showed evidence of hepatic dysfunction, which was reversible in most cases. There were no cases of CHF reported, although all of the patients had previously been treated with anthracyclines. Two patients had reversible arrhythmia and four showed minor EKG changes. Twenty-one of the 52 patients who achieved CR underwent bone marrow transplantation (BMT). Eleven patients relapsed at a median of 4 months (range 1-31) after transplantation, and three patients died while in CR. Seven patients have been in continuous complete remission for a median of 36 months (range 26-42 months) at the time of the report. Thirty-one patients were not entered into the BMT program, 25 of them due to relapse at a median of 4 months (range 1-25). The authors noted the poor prognosis of

patients who received standard maintenance chemotherapy and have devised a different IDA plus Ara-C schedule to minimize toxicity.

Testi et al (1992) reported the early results of the Italian ALL-R87 study, a reinduction protocol of IDA plus intermediate-dose Ara-C for children with primary refractory or relapsed ALL treated in the AIEOP 88 and 91 protocols. Reinduction was followed by short consolidation therapy and autologous or allogeneic BMT. Twenty-four patients (77%) achieved complete remission (CR), 8 patients relapsed early, and two were removed from the study. Fourteen (45% of the original 31 patients) underwent BMT and seven of these patients (22%) were still in continuous complete remission at a median follow-up of 18 months. Toxicity from induction therapy consisted of severe myelosuppression complicated by infections and hemorrhages. Extrahaematologic toxicity was predominantly gastrointestinal with mucositis and diarrhea. No cardiac toxicity greater than Grade 1 was reported. The authors confirmed that it is possible to achieve CR even in ALL children who failed on an initial intensive regimen and note the need for other modalities of post-remission therapy for patients lacking an HLA-identical donor.

GIMENA/AIEOP protocol ALL R-87 (**Giona et al 1994**) consisted of an induction phase with IDA plus intermediate-dose cytarabine, followed by a consolidation phase and BMT. CR was achieved in 97/147 patients (66%) with a CR rate of 77% in children versus 51% in adults (P <0.01). All patients experienced profound myelosuppression and associated infections and hemorrhage. Gastrointestinal toxicity included nausea and vomiting, diarrhea, and mucositis. No CHF or significant arrhythmias were observed; one patient experienced asymptomatic decrease of LVEF to 38% from 64% pretreatment. Forty-eight responders underwent BMT. Probability of event-free survival (EFS ± SE) was 10.2 ± 3.1% at 56 months. EFS was 14.3 ± 4.51% at 56 months for children versus 3.8 ± 3.41% at 37 months for adults (P <0.0001). Among patients treated in first relapse, EFS was 14.2 ± 7.79% for patients with CR > 18 months versus 6.6 ± 3.17% for those with CR < 18 months (P <0.0001). Projected disease-free survival (DFS ± SE) was 15.4 ± 4.61% at 55 months for all responders and 43.3 ± 14.34% at 52 months for allografted patients. Projected overall probability of survival ± SE was 18.8 ± 4.13% at 56 months.

Bernstein et al (1997) reported the results of a Paediatric Oncology Group study of IDA + Ara-C as reinduction therapy for children with multiple recurrent or refractory ALL. Eighty-two patients were entered. Overall, 30 patients (37%) achieved a complete remission; however, these were mostly of brief duration. There were 14 deaths, 9 of them early from documented or presumed bacterial or fungal sepsis, for an overall mortality rate of 17% in this group of heavily pretreated patients. Grade 3 or 4 toxicities included nausea, vomiting, diarrhea, and chemical conjunctivitis despite the use of prophylactic dexamethasone drops. A single patient who had previously received 175 mg/m^2 doxorubicin developed an asymptomatic decrease in shortening fraction following 2 cycles of IDA + Ara-C induction therapy.

Giona et al (1997) also reported on a subset of children in early bone marrow relapse treated in the Italian ALL R-87 protocol, referenced above: 55/73 (75.3%) children achieved CR. The response rate was significantly higher for children with a first CR duration ≥ 12 months (P=0.0005) and for those with a WBC count at relapse < 20 x 10^9/L

(P = 0.004). The estimated DFS ± SE at 82 months was 0.18 ± 0.05 for all responders, and 0.70 ± 0.14 for allotransplanted patients versus 0.05 ± 0.05 for those autografted (P = 0.001). For all enrolled children, the estimated probabilities for survival ± SE and event-free survival ± SE at 83 months were 0.16 ± 0.07 and 0.13 ± 0.04, respectively.

Neuendank et al (1997) reported on the results of a phase II study evaluating the safety and efficacy of a 48-hour continuous infusion of single-agent idarubicin (24 mg/m^2) in 51 paediatric patients (1 to 16 years of age) with prognostically poor recurrences of ALL. Patients also received simultaneous central nervous system prophylaxis with either intrathecal methotrexate alone (3 patients) or with intrathecal methotrexate, cytarabine and prednisone (31 patients), while 17 children received no prophylaxis therapy. Complete and partial remission was seen in 5 and 20 patients (49%), respectively. Most patients experienced severe, grade 3 or 4 hematologic toxicity and high rates of system infection causing treatment delays. Non-hematologic toxicities including acute cardiac reactions were transient and moderate, although grade 4 toxicity was reported in 3 children [severe stomatitis (1 patient) and elevated SGOT and SGPT (2 patients)].

Giona et al (1998) reported on yet another subset of patients treated in the Italian ALL R-87 protocol, this time in 57 patients < 55 years with ALL in second or third bone marrow relapse or refractory to first-line therapy. CR was achieved in 41/57 patients (72%). The CR rate was significantly higher in patients < 15 years at diagnosis and at time of treatment compared to those aged ≥ 15 (84% vs 50%, p = 0.01 and 85% and 54%, p = 0.02, respectively). No CHF or significant arrhythmias were observed. Nineteen of 41 responders (46.3%) underwent bone marrow transplant (BMT) (10 autologous and 9 allogeneic). The estimated probabilities of EFS ± SE and survival ± SE at 6 years were 0.13 ± 0.05 and 0.20 ± 0.06, respectively, for all enrolled patients. Univariate analysis showed that children had a better EFS rate compared to adults. The estimated probability of DFS ± SE at 6 years was 0.18 ± 0.07 for all responders. No differences in DFS were observed between patients who received allogeneic or autologous BMT (0.33 ± 0.16 vs 0.25 ± 0.15). Among patients treated in second or third relapse, a first CR length ≥ 48 months favorably influenced both DFS (p = 0.014) and EFS (p = 0.018).

Leahey et al (2000) reported on a novel multiagent chemotherapy regimen including idarubicin designed to improve EFS after bone marrow relapse in paediatric ALL conducted at the Children's Hospital of Philadelphia. Induction was followed by consolidation, reconsolidation and maintenance therapy for responders. The CR induction rate was 95%. Significant infectious complications occurred during induction for 11/21 patients (52%), including one patient who died of sepsis. With a median follow-up from date of relapse of 49 months in survivors, the actuarial EFS based on intent-to-treat was 75%. There were three toxic deaths in patients in CR and two deaths from relapse."

Assessor's comment:

*The assessor would agree with a general statement that anthracyclines, in general, are well established in the treatment of **ALL** (including remission induction after first or further relapses) as long as cumulative anthracycline dose still allows their administration in an individual patient..*

Concerning the statement of the MAH "The data in the published reports support the efficacy of idarubicin in paediatric patients with ALL, confirming that the use of idarubicin is well established in current paediatric clinical practice.", however, both the data on file and those published are indicating in a completely different direction:

First, none of these trials has been conducted or published recently. Rather, the most recent publication has an age of more than 10 years.
*Second, with the exception of a single trial (*Feig et al (1996) - doi: 10.1002/(SICI)1096-911X(199612)27:6<505::AID-MPO1>3.0.CO;2-P; see also http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1096-911X(199612)27:6%3C505::AID-MPO1%3E3.0.CO;2-P/pdf , *none of the trials were comparing idarubicin with (standard) daunorubicin. The benefit risk of the one and only comparison is, as already outlined above, negative for both idarubicin dose intensities investigated.*
Third, idarubicin is not explicitly mentioned in relevant, current therapeutic guidelines. The latter is the criteria the assessor would set out for claiming that e.g. idarubicin (or liposomal daunorubicin, doxorubicin, mitoxantron etc.) is "well established in current paediatric clinical practice."

In summary, the overall efficacy conclusion of the MAH concerning (childhood) ALL cannot be followed. The proposal of the MAH (of the originator product) to add (or to modify depending on the national/regional SmPC under discussion) an explicit second line (childhood) ALL indication to the not harmonized SmPCs of the CMSs (and RMS) is rejected by the RMS of this work sharing procedure.

An other issue to criticize - concerning the efficacy conclusion on ALL, or more specifically, oral idarubicin in childhood leukemias (in general) is that the assessor could imagine – actually based on the data as submitted – that there could be a kind of "semi-palliative last line treatment" of younger patients with ALL comparable with the indication granted (in the RMS) to Zavedos oral in elderly AML patients (who are not always amenable to a full-intensity remission induction therapy). Such an, at least potential, indication of the oral idarubicin products in childhood ALL (and AML) has not been discussed seriously by the MAH.

*Concerning **childhood AML** the assessor agrees with the efficacy conclusion of the MAH that "the **data on file** for paediatric patients is limited, and includes several studies of the oral formulation administered in children with ANLL/AML for which there no current approved indication." For childhood AML, however, the MAH has **not presented a literature review** comparable to that presented for ALL. This is rather surprising taking into account the following wording of a current German guideline - http://www.awmf.org/uploads/tx_szleitlinien/025-014.pdf, a guideline specific for AML and ALL in childhood :*
Original language: „AML|Chemotherapie|Induktionstherapie: …Die Einführung der ADE (Ara-C, Daunorubicin, Etoposid) -Induktion in der Studie AML-BFM-83 ergab eine signifikante Verringerung der Rezidivraten im Vergleich zur Vorgängerstudie. Inzwischen wird an Stelle des Daunorubicins das Idarubicin oder liposomal formuliertes Daunorubicin eingesetzt."
*Translation: AML/Chemotherapy/Induction treatment: … The introduction of the ADE (…) in trial AML-BFM-83 resulted in a significant reduction of the relapse frequency compared to the preceding trial. **By now, in place of daunorubicin idarubicin or liposomal daunorubicin is used.***

To understand the latter statement of the (German AWMF) guideline a literature review is required. The decisive trials for this statement are the sequence of the AML-BFM 93 - doi:10.1038/sj.leu.2403920 as well as Leukemia 15, 348–354, 2001 (or http://www.nature.com/leu/journal/v15/n3/pdf/2402046a.pdf, (AML-BFM 98 - http://abstracts.hematologylibrary.org/cgi/content/abstract/104/11/1793), and (most recently

presented) AML-BFM 2004 - http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/181 - trials. In this sequence of BFM trials, daunorubicin has been replaced by idarubicin mainly for the following reason (deriving from AML-BFM-93):

"The most important result comparing idarubicin and daunorubicin during induction in our study was the blast cell reduction on day 15 with only 17% of AIE patients presenting with >5% blasts compared to 31% after ADE. This was in line with our results of study AML BFM 87, where all patients were treated with ADE and where 31% of the patients presented >5% blasts on day 15. However, the difference in the number of patients with >5% blasts on day 15 after AIE compared to ADE was restricted to the (morphologically defined) high risk patients (P = 0.007) and was not significant in standard risk patients. This seems to indicate that an induction with daunorubicin may be already sufficient for standard risk patients, but not for high risk patients and that mainly high risk patients benefit from the treatment with idarubicin. - Leukemia 15, 348–354, 2001 (or http://www.nature.com/leu/journal/v15/n3/pdf/2402046a.pdf)- "

Accordingly, idarubicin was the standard anthracycline used in all subsequent BMF trials.

Thus, it may be recommended to the MAH to update his data on file, and to discuss standard of care in childhood AML as set out, among others, by the BMF study group, and (resulting) current treatment guidelines valid in the RMS (or any other valid for the CMSs involved).

- **PK Data in Childhood**

In addition to the reports and publications intended to support the discussion of efficacy by the MAH, additional 4 sub-studies of the studies already displayed in the preceding sections concerning PK in children are discussed by the MAH as follows:

> "The idarubicin Core Data Sheet (2008) includes the indication of second-line treatment of ALL in children for the injectable formulation; however, no pharmacokinetic (PK) data in children are provided. The MAH has performed a review of internal data and the published literature and identified 4 relevant studies, the PK portions of which are summarized below.
>
> Pui et al (1988)
>
> Fifteen (15) children with acute leukemia in relapse were treated with idarubicin orally for 3 consecutive days in dosages ranging from 30 to 50 mg/m^2 at 19-21 day intervals. Plasma samples for pharmacokinetics were obtained for each patient during the first 3 day cycle before treatment and 1, 2, 4, 6, 8, 12 and 24 hr after the 1st dose and 24 hr after the 2nd and 3rd doses. Results indicated that the median terminal half life of idarubicin was 9.2 hr (range: 6.4-25.5 hr). Median dose normalized AUC_{0-24} was 2.4 (range: 0.7 – 3.8) ng/hr/mL/mg. Significant accumulation of the active metabolite, idarubicinol, was seen over the 3 day treatment period.
>
> Reynolds (1987) – FCE report IMI 30/79925i
>
> Seventeen (17) patients entered the study, 15 of whom had leukemia and 2 other tumors. Patients received idarubicin orally in dosages ranging from 30 to 50 mg/m^2 for 3 days. Pharmacokinetics were characterized in leukemia subjects after the first oral dose of idarubicin. Serum samples were obtained for PK at 1, 2, 3, 4, 5, 6, 12, 24, 48 and 72 hours

after dosing. Results indicated a half life for idarubicin of 11.2 ± 6.0 hr, tmax of 4.8 ± 2.0 hr, and dose normalized AUC_{0-24} of 2.3 ± 1.2 ng/hr/mL/mg. Significant accumulation of the active metabolite, idarubicinol, occurred as indicated by a ratio of $AUC_{idarubicinol}/AUC_{idarubicin}$ of 3.8 over the first 24 hr.

Gams & Gerber (1990) – FCE report IMI 30/615i

Twenty nine (29) patients entered the study; PK was measured in 13 of these (4 solid tumors, 9 leukemia) at doses ranging from 30 to 150 mg/m^2. Idarubicin was given in 3 day cycles followed by 21 days off treatment. Samples were obtained for PK on Day 1 at 0 (pre-dose), 5, 10, 30, 60, 120, 240, 480 min after dosing, on Day 2 at 0, 2, 4, and 8 min after dosing, on Day 3 at 0, 2, 4, 8 hr after dosing, on Days 4, 5, 6, and 7 at 72, 96, 120 and 144 hr. Results indicated considerable intersubject variability in PK, and data was considered insufficient to relate Cmax and AUC to hematologic effect.

Tan et al (1987)

Forty-two (42) evaluable children 1-19 years old were enrolled. Twenty-seven had leukemia and 15 had various solid tumors. The drug was administered IV in escalating doses of 10 to 40 mg/m^2/course in 3 equal fractions over 3 consecutive days at 14- to 21-day intervals. Pharmacokinetics were measured in 7 patients receiving from 15 to 40 mg/m^2/course of treatment. In most patients, the plasma clearance of idarubicin fit a 3-compartment model with a harmonic mean half-life of 2.4 min, 0.6 h, and 11.3 h for the α, β, and γ elimination phases, respectively. The median terminal half life of idarubicin was 8.5 hr (range: 3.6 – 26.4 hr). Idarubicinol was the only metabolite detected in the plasma and it accumulated during the 3 days of therapy and it exhibited a median half life of 43.7 hr (range: 27.8-131 hr).

PK Conclusions

On the basis of the results reported in these 4 studies, the MAH proposes to include the following text in Section 5.2 of the idarubicin EU SmPC:

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2/3 day course of treatment, showed a median idarubicin half life of 8.5 hr (range: 3.6 – 26.4 hr). The active metabolite, idarubicinol, accumulated during the 3 day therapy, exhibiting a median half life of 43.7 hr (range: 27.8-131 hr). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2/3 day course of treatment, showed a median terminal half life of idarubicin of 9.2 hr (range: 6.4-25.5 hr). Significant accumulation of idarubicinol was seen over the 3 day treatment period."

Assessor's comment:

There are no objections to amending sec. 5.2 by additional PK data in children. However, before doing so, the MAH should discuss PK data in children relative to the available adult data. The following points for clarification are, therefore proposed:

- The applicant should set the PK data in children in relation to adult data and discuss differences, if observed. For the oral administration the MAH should clarify specifically whether there are clinically relevant differences in absorption/bioavailability in adults, children and adolescents.

- **Safety update and safety conclusion in children**

For preparing this submission, the MAH made a search in his safety database for all medically confirmed idarubicin cases in paediatric patients (where age was reported as ≤ 17 years) reported from product launch through 31 May 2010. The international birth date for idarubicin is 29 November 1989.
This search of the MAH's safety database identified a total of 2,819 medically confirmed idarubicin cases (5,799 adverse events) entered through 31 May 2010. Of these cases, 118 (4.2%) reporting 274 events involved patients ≤ 17 years of age. The patients ranged in age from 0.8 to 17.0 years; the mean (±SD) age was 10.7 (±5.0) years. Leukemias were the most commonly reported indications for idarubicin, AML being the most common followed by ALL. The majority of the cases (103) were serious.

To keep the AR brief this safety analysis as displayed in the clinical overview is not outlined here at full length. In place, the overall safety conclusion of the MAH based on this search is sufficient and reads:

> "This cumulative review of idarubicin medically confirmed paediatric cases in the MAH's safety database through 31 May 2010 revealed 118 cases representing 4.2% of the total number of medically confirmed idarubicin cases in the database. Overall, there did not appear to be significant or qualitative findings to suggest a safety profile in paediatric patients that is different from the overall safety profile for idarubicin."

Furthermore, it is argued that the published literature does not directly examine the relationship between idarubicin and the incidence of cardiotoxicity in children. The cardiotoxic effects of anthracyclines including doxorubicin and daunorubicin in children have been demonstrated in a number of studies and well documented in the literature, and suggest younger age at diagnosis and treatment as a risk factor.
On the basis that idarubicin is similar to daunorubicin in pharmacology and toxicology, exhibits similar cardiotoxicity to that of other anthracyclines, and is indicated for use in children, the MAH updated the idarubicin Core Data Sheet in May 2007 to include the following class warning/precaution statement regarding increased susceptibility of children to anthracycline-induced cardiac toxicity:

In infants and children there appears to be a greater susceptibility to anthracycline-induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed.

Assessor's comment:

The conclusion of the MAH that safety profile (eventually except cumulative cardiotoxicity) in children does not differ amenable from adults is endorsed based on the data as presented. Of note is that the by far most commonly reported indication in the case reports of children searched is AML (65%) followed by ALL (10%). Also these safety data, allowing some indirect conclusion on exposure, underline the surprise of the assessor that the MAH suggests to add childhood ALL but not childhood AML to the SmPC.

A greater susceptibility to anthracycline-induced cardiac toxicity in infants and children is actually a "class effect" of anthracyclines described in SmPCs of daunorubicin, or doxorubicin, containing MPs. A warning as proposed for sec. 4.4 of idarubicin by the MAH is, therefore, endorsed provided that the indication is not explicitly limited to adults only.

3. Discussion on clinical aspects

Zavedos and Zavedos oral have granted national MA in the RMS of this work sharing procedure (DE) since 1990. The nationally granted SPCs have not been subject of an EU wide harmonization.

The indications of these products is limited (in the RMS) to **AML in adults** only. In terms of an article 45 work sharing procedure the RMS involved, thus, would expect that the MAH would discuss now, about 20 years later the benefit risk of Zavedos and Zavedos oral in **AML of childhood** just for the reason that general treatment principles of childhood AML follow those developed in adults.

Concerning both AML and ALL (of childhood) the MAH is of the opinion that the "data on file" (i.e. MAH sponsored trials submitted within this procedure) is limited. Based on a literature review performed for ALL of childhood, the MAH is concluding that *"the data in the published reports support the efficacy of idarubicin in paediatric patients with ALL, confirming that the use of idarubicin is well established in current paediatric clinical practice."*

The RMS is not endorsing the conclusion of the MAH. Rather, the data on file, the published reports and the guidelines consulted by the RMS rather suggest that the benefit risk of idarubicin in ALL is negative compared to daunorubicin.

Based on these data the MAH proposes to add the following indication:

Acute lymphocytic leukemia (ALL) as second-line treatment in adults and children

As the introduction of an **adult** indication is beyond the scope of article 45, the RMS is rejecting the adult indication. The MAH should consider performing an article 30 procedure in order to harmonize the SmPC EU wide, and in order to assess the available data in adults.
The introduction of a **paediatric** ALL indication (within this article 45 procedure) is rejected by the RMS since the trials (and publications) submitted allow the conclusion that the benefit risk, compared to daunorubicin (in second line treatment), is negative.

Based on a literature search performed by the RMS, the RMS concludes that, based on the trials performed by the BMF study group idarubicin has replaced daunorubicin as the standard anthracycline in (first) remission induction combination treatment of **AML of childhood** – at least in the RMS. The MAH is invited to perform his own literature review, discuss the conclusion of the RMS, and to propose an indication for Zavedos i.v. in **AML of childhood**.

Finally, the submitted data allow the conclusion that oral administration of idarubicin is at least feasible in children and adolescents.
As well as in adults, however, oral administration of a substance with a very narrow therapeutic window has serious draw backs due to the high inter-individual variability of absorption. Thus, oral administration cannot be recommended for the first line treatment of children with leukaemias. However, oral idarubicin is an active treatment both in adults and in children. The

"utility" of oral Zavedos in children, however, is not discussed by the MAH. Therefore, the MAH should discuss potential therapeutic places of oral Zavedos both in ALL and AML of childhood.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH of the innovator products for idarubicin (Zavedos and Zavedos oral) proposes to change/amend the indication by an adult and a paediatric (second line) indication in ALL. The MAH is not proposing an indication in AML of childhood.

Based on the data submitted by the MAH, a literature search performed by the RMS, and relevant guidelines consulted by the RMS, the RMS concludes that the proposed indication in ALL should not be granted.
In contrast, idarubicin (besides DaunoXome) is the state of the art first line anthracycline to be used in children with AML (at least those with high risk AML). Therefore, the MAH should update his data on file and propose a first line indication in children with AML taken into account current therapeutic guidelines.

In addition, the MAH should discuss reasonable paediatric indication for oral idarubicin since the data submitted suggest that oral administration in children is feasible, and that oral idarubicin is active in leukaemias of childhood.

In the case that SPC will be amended by paediatric indication(s) (sec. 4.1), the proposals made by the MAH for sec. 4.2 (Posology), 4.4 (Warnings) and 5.3. (PK) are reasonable and should be performed. The precise wording still needs some clarification and a further discussion.

- **Recommendation**

Based on the data submitted, the MAH should provide

- a literature review comprising also relevant current guidelines for **AML in childhood**
- a summary of comparative PK in adults vs. children (including oral administration)

as part of this work sharing procedure. (see section VI "Request for supplementary information")

- **MS Comments**

On the Rapporteur's overall conclusion and recommendation as of the day 70 draft Paediatric AR (PdAR) comments were received from IE, NL, SE, and UK. In general, with the exception of NL concerning the ALL indication, they endorsed the Rapporteur's conclusion.

In detail, they read as follows:

- **IE**

In relation to the above paediatric worksharing procedure we generally concur with the RMS assessment report.

We agree that an article 30 referral should be undertaken if the product information is not harmonised.

For information Zavedos powder for solution for injection is Nationally licensed for:

In the treatment of relapsed acute lymphoblastic leukaemia (ALL) as second line treatment in adults and children.

In relation to the questions: The MAH should provide a fully literature review which should be fully assessed prior to proposing wording for AML in childhood, therefore question 2 should be deleted for the present.

The MAH should provide a literature review comprising also relevant current guidelines for **AML in childhood**. With this literature review the MAH should discuss the conclusion of the RMS that idarubicin (besides DaunoXome) is the state of the art first line anthracycline to be used in children with AML (at least those with high risk AML). The MAH should propose a first line indication in AML of childhood.

We agree with the other aspects of the SPC

RMS Assessor's comment:

The request to delete question 2 is not fully understood. It is assumed that rather question 3, relating to the precise wording of the indication, could be meant. Provided that the latter interpretation is correct, the RMS is of the opinion that there are no objections to asking the MAH for such a proposal. The precise wording to propose, finally, to all CMS (within a public AR) has, however, still to be discussed on the basis of the information provided (in response to question 2).

- **NL**

ALL:
The indication "Acute lymphocytic leukemia (ALL) in adults and children, second-line treatment" is granted for idarubicin in the Netherlands. In a combined UK - Dutch study for relapsed ALL in children (ALL-R3 version Sep 2007), patients were initially randomized to be treated with either idarubicin or mitoxantrone, during the induction phase of the treatment. However, the idarubicin arm was deleted from the study due to significant better survival and less toxicity in patients treated with Mitoxantrone. However, although also other drugs (anthracyclines) are used, idarubicine is still an important treatment option that is used in children diagnosed with (relapsed) ALL (see Van den Berg et al.,Paediatric Blood&Cancer 2010;9999:1-7). The choose of the drug that is to be used for the treatment of pediatric patients, is not only depended on the efficacy of idarubicin in comparison to other drugs, also its cardiotoxicity in comparison to other antracyclines should be taken into consideration. Differences in cardiotoxicity might be seen, as the doses of idarubicin are usually lower than for other anthracyclines. For the final discussion regarding the relapsed ALL indication, a complete literature review, regarding the benefit and toxicity of idarubicin in comparison to other antracyclines should be provided (comparative animal studies might be included). The review should include finished and recent clinical trial in pediatric (relapsed) ALL.
The conclusion of the RMS that the ALL indication should not be granted is not endorsed

AML:
At the moment Idarubicin is not indicated for the treatment of children with AML, in the Netherlands.

International, commonly used paediatric induction therapy regimens against AML, use cytarabine and an anthracycline in combination with other agents such as etoposide and/or thioguanine. For example, the Children's Cancer Group (CCG) intensively-timed dexamethasone, cytarabine, thioguanine, etoposide, and rubidomycin (DCTER) and idarubicin (IDA)-DCTER regimens utilized cytarabine, daunorubicin or idarubicin, dexamethasone, etoposide, and thioguanine given as two 4-day treatments separated by 6 days.

The German Berlin-Frankfurt-Munster Group studied cytarabine plus etoposide with either daunorubicin or idarubicin (ADE or AIE) administered over 8 days. The United Kingdom Medical Research Council (MRC) 10 Trial compared induction with ADE versus cytarabine and daunorubicin administered with thioguanine (DAT).

The anthracycline that has been most used in induction regimens for children with AML, is daunorubicin, though idarubicin and the anthracenedione mitoxantrone have also been used.

The RMS has asked the MAH to update his data on file and provide a literature review comprising also relevant current guidelines for AML in childhood. The question of the RMS is endorsed; definitive conclusions regarding approval of the AML indication for children will be drawn after the additional information is assessed.

The following questions of the RMS are endorsed:

1) The MAH should set in relation the PD data in children to adult data and discuss differences, if observed. In addition for the oral administration, the MAH should clarify specifically whether there are clinically relevant differences in absorption/bioavailability in adults, children and adolescents.
2) The MAH should provide a literature review comprising also relevant current guidelines for AML in childhood. With this literature review the MAH should discuss the conclusion of the RMS that idarubicin (besides DaunoXome) is the state of the art first line anthracycline to be used in children with AML (at least those with high risk AML).

Question three should be modified:

3) The MAH should submit data confirming a positive benefit risk ration of (second line) idarubicin compared to daunorubicin in ALL of childhood.

N.B. The oral idarubicin formulation is not registrated in the Netherlands.

Points for clarifications (Other concerns)

The assessment and the following questions of the rapporteur are endorsed.

1) The MAH should set in relation the PD data in children to adult data and discuss differences, if observed. In addition for the oral administration, the MAH should clarify specifically whether there are clinically relevant differences in absorption/bioavailability in adults, children and adolescents.
2) The MAH should provide a literature review comprising also relevant current guidelines for AML in childhood. With this literature review the MAH should discuss the conclusion of the RMS that idarubicin (besides DaunoXome) is the state of the art first line anthracycline to be used in children with AML (at least those with high risk AML).

Question 3 should be modified, the cardiotoxicity and the use of idarubicin in recent clinical trials should be added.

3) The MAH should submit data confirming a positive benefit risk ration of (second line) idarubicin compared to daunorubicin in ALL of childhood. The literature review should be extended. Not only should the efficacy of idarubicin in comparison to other anthracyclines, but also its cardiotoxicity in comparison to other drugs be addressed. Moreover, the use of idarubicin in recent clinical trials for children with relapsed ALL should be included in the review.

One additional question regarding the mode of administration:

4) The MAH should address the differences in response and PK related to upregulation of MDR enzymes and by doing so additionally sort out the mode of administration.Which might be altered due to overexpression of MDR enzymes in the the intestine of heavily treated patients influencing oral absorption.

On behalf of the MEB

RMS Assessor's comment:

It is/was foreseeable that not all CMS will agree with the conclusion of the RMS that the (paediatric) indication in ALL should not be granted. Therefore, and since also the adult ALL indication is not licensed in the RMS (but not the subject of this article 45 procedure), an article 30 procedure has been proposed by the RMS. If no agreement in-between CMS (cf. also comment SE below) can be achieved within this article 45 procedure, the conduct of an article 30 procedure seems to be unavoidable.

The endorsement, request for rewording, and additional questions has been implemented in the (by day 89 updated) LoQ below.

- **SE**

SE agrees with the overall conclusions of the Rapporteur.
Very recently published studies may further support these conclusions:

The ALL indication may thus be further questioned based on the publication by Parker and co-workers in December 2010, of a randomised multicenter study in 216 children with first relapse of ALL showing a 3-year overall survival of 45.2% for idarubicin vs. 69.0% for mitoxantrone (p=0.004).

The potential AML indication is supported also by the publication by Abrahamsson and co-workers in January 2011, showing that idarubicin is an option for first line treatment according to the AML 2004-protocol of the Nordic Society for Paediatric Haematology and Oncology, with Sweden, Denmark; Finland, Norway and Iceland as participating countries.

References:

Parker C, Waters R, Leighton C, Hancock J, Sutton R, Moorman AV, Ancliff P, Morgan M, Masurekar A, Goulden N, Green N, Révész T, Darbyshire P, Love S, Saha V. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet. 2010 Dec 11;376(9757):2009-17. Epub 2010 Dec 3. PubMed PMID: 21131038; PubMed Central PMCID: PMC3010035.
(Free full text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010035/?tool=pubmed)

Abrahamsson J, Forestier E, Heldrup J, Jahnukainen K, Jónsson OG, Lausen B, Palle J, Zeller B, Hasle H. Response-guided induction therapy in pediatric acute myeloid leukemia with excellent remission rate. J Clin Oncol. 2011 Jan 20;29(3):310-5. Epub 2010 Dec 13. PubMed PMID: 21149663.
(http://jco.ascopubs.org/content/29/3/310.long)

On behalf of the Medical Products Agency

RMS Assessor's comment:

The MAH is advised to update the data on file/literature review (see LoQ below)) also by the publications quoted by the Swedish colleagues.

- **UK**

The conclusions of the RMS are endorsed. There are no additional comments.

On behalf of the MHRA

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions:

1. The MAH should set in relation the PK data in children to adult data and discuss differences, if observed. In addition for the oral administration, the MAH should clarify specifically whether there are clinically relevant differences in absorption/bioavailability in adults, children and adolescents.
2. The MAH should provide a literature review comprising also relevant current guidelines for **AML in childhood**. With this literature review the MAH should discuss the conclusion of the RMS that idarubicin (besides DaunoXome) is the state of the art first line anthracycline to be used in children with AML (at least those with high risk AML).
3. The MAH should propose a first line indication in AML of childhood.
4. The MAH should submit data confirming a positive benefit risk ration of (second line) idarubicin compared to daunorubicin in ALL of childhood. The literature review should be extended. Not only should the efficacy of idarubicin in comparison to other anthracyclines, but also its cardiotoxicity in comparison to other drugs be addressed. Moreover, the use of idarubicin in recent clinical trials for children with relapsed ALL should be included in the review.
5. The MAH should discuss a potential therapeutic places of oral idarubicin in ALL and AML of childhood.
6. The MAH should address the differences in response and PK related to upregulation of MDR enzymes and by doing so additionally sort out the mode of administration. Which might be altered due to overexpression of MDR enzymes in the the intestine of heavily treated patients influencing oral absorption.

VII. ASSESSMENT OF RESPONSES (AS OF OCTOBER 3RD, 2011)

Question # 1

1. The MAH should set in relation the PK data in children to adult data and discuss differences, if observed. In addition for the oral administration, the MAH should clarify specifically whether there are clinically relevant differences in absorption/bioavailability in adults, children and adolescents.

Response of the MAH

The pharmacokinetic properties of idarubicin after oral and intravenous administration have been studied in both adult patients and paediatric patients with solid tumors or acute leukemia. A review of the published literature revealed five key adults studies and three key paediatric studies in which pharmacokinetic parameters were measured in each patient population. Table 1 below represents mean pharmacokinetic parameters from the published literature in both patient populations with various types of cancer receiving intravenous or oral doses of idarubicin.

Table 1. Mean pharmacokinetic parameters in Patients with Various Types of Cancer Receiving Intravenous or Oral Doses of Idarubicin

Reference	No. of patients	Dosage (mg/m^2)	C_{max}[a] (µg/L)	t_{max} (h)	Vd[a] (L/m^2)	CL Reported	CL ($L/h/m^2$)	Bioavailability (%)
Intravenous Idarubicin								
Adults:								
Gillies et al. (1987)	20	15	---	---	1533	98.7 $L/h/m^2$	98.7	---
Lu et al. (1986)	9	10 – 12.5	---	---	63.9L/kg	1.9 l/kg/h	71.4	---
Smith et al. (1987)	28	15	---	---	---	89.2 l/h	89.2	---
Speth et al. (1986)	7	10	49	---	2250L	---	---	---
Paediatrics:								
Reid et al. (1990)	21	10 - 15	---	---	562	679 $ml/min/m^2$	41	---
Tan et al. (1987)	7	5 – 13.3	---	---	---	299-549 $ml/min/m^2$	18 - 33	---
Oral Idarubicin								
Adults:								
Gillies et al. (1987)	11	30 – 70	12.65	2.7	1718	107.9 $L/hr/m^2$	107.9	29
Lu et al. (1986)	10	10	---	1	---	8.4 $l/kg/m^2$	39	---
Pannuti et al. (1986)	12	10 – 15	4-10	---	---	---	---	---
Smith et al (1987)	5	15	---	---	---	---	---	24
Speth et al. (1986)	7	30	---	2-4	---	---	30	---
Paediatrics:								
Pui et al. (1988)	15	30 – 50	10.6[b]	6	---	---	---	---

a: unless otherwise stated
b: median $C_{max,\ 40mg}$ (ng/ml)
Abbreviations: CL=clearance; $C_{max\ 40mg}$=peak plasma concentration after an oral dose of 40 mg/m^2; t_{max}=time to peak concentration after oral administration; VD=volume of distribution.

In adults, idarubicin is absorbed rapidly following oral administration with a lag time of 0.5 hours before concentrations can be detected in plasma (Gillies et al, 1987; Speth et al, 1986). Peak plasma concentrations of 4-12.65 mcg/mL were attained 1 to 4 hours after ingestion of idarubicin 10 to 60 mg/m^2 in adults. Similarly, a median peak concentration of 10.6 mcg/mL (range 2.7-16.7 mcg/mL) were reportedly attained 6 hours (range 1-8 hours) after oral administration of 40 mg/m^2 in paediatric patients (Pui et al. 1988). Bioavailability varies between adult patients with an average of 26.5 hours. Data on bioavailability in the paediatric population is unknown. Although a biphasic pattern of plasma idarubicin clearance was observed in some studies (Gillies et al, 1987; Lu et al. 1986; Speth et al, 1989), a triphasic plasma clearance has also been reported in both adult and paediatric populations, with a rapid initial (α) distribution phase, an intermediate (β) distribution phase and then a much slower elimination (γ) phase (Smith et al. 1987; Reid et al. 1990; Tan et al. 1987). Idarubicin has a very large volume of distribution in both adults and paediatric patients, suggesting that much of the drug is bound to tissues.

Idarubicin was no longer detectable in plasma 72 hours after intravenous administration of 15 mg/m^2 in adults due to biotransformation of idarubicin to idarubicinol in the liver (Gillies et al. 1987). In both adults and children, the plasma concentration of idarubicinol consistently exceeded that of idarubicin. About 2-fold more metabolite is produced following oral compared with intravenous administration, probably as a result of first-pass metabolism (Smith et al. 1987; Speth et al. 1986). In adults, the reported mean elimination half-life for idarubicin (range 12-34.8 hours) is longer than that reported in the paediatric population (range 9.2-17.6 hours). A prolonged half-life of idarubicinol was noted in both adult and paediatric patients with its accumulation in plasma on repeated daily administration (Speth et al. 1986; Tan et al. 1987). Total body clearance rates for idarubicin of 30-107.9 L/h/m^2 have been noted for adults while the clearance reported for the paediatric population were on the lower range reported from 18-33 L/h/m^2.

Despite variability in pharmacokinetic parameters between patients and studies and relatively small number of subjects evaluated, the majority of studies provided similar overall findings, although data suggests total body clearance may be lower in the paediatric population than in the adult population.

Literature Review of Pharmacokinetics: Paediatric Patients

The idarubicin Core Data Sheet (CDS) (2008) states that intravenous (IV) idarubicin is indicated for treatment of AML in adults for remission induction as first-line therapy or for remission induction in relapsed or refractory patients; oral idarubicin is indicated for treatment of AML for remission induction in previously untreated, relapsed or refractory patients whenever IV idarubicin cannot be used. However, no PK data in children are provided. The MAH has performed a review of internal data and the published literature and identified 4 relevant studies, the PK portions of which are summarized below.

Pui et al (1988)

Fifteen (15) children with acute leukemia in relapse, refractory to conventional therapy, were treated with idarubicin administered orally for 3 consecutive days in dosages ranging from 30 to 50 mg/m^2 at 19-21 day intervals. Plasma samples for pharmacokinetics were obtained for each patient during the first 3 day cycle before treatment and 1, 2, 4, 6, 8, 12 and 24 hr after the 1st dose and 24 hr after the 2nd and 3rd doses. Results indicated that the median terminal half life of idarubicin was 9.2 hr (range: 6.4-25.5 hr). Median dose normalized area under the concentration-time curve for the first 24 hours AUC_{0-24} was 2.4 (range: 0.7–3.8) ng/hr/mL/mg. Significant accumulation of the active metabolite, idarubicinol, was seen over the 3-day treatment period.

Reynolds (1987) – FCE report IMI 30/79925i

Seventeen (17) patients entered the study, 15 of whom had leukemia and 2 other tumors. Patients received idarubicin orally in dosages ranging from 30 to 50 mg/m^2 for 3 days. Pharmacokinetics were characterized in leukemia subjects after the first oral dose of idarubicin. Serum samples were obtained for PK at 1, 2, 3, 4, 5, 6, 12, 24, 48 and 72 hours after dosing. Results - The nature of the summary statistics used in this study were not clearly identified in the report. - indicated a half life for idarubicin of 11.2 $\pm$ 6.0 hr, t_{max} of 4.8 $\pm$ 2.0 hr, and dose normalized AUC_{0-24} of 2.3 $\pm$ 1.2 ng/hr/mL/mg. Significant accumulation of the active metabolite, idarubicinol, occurred as indicated by a ratio of $AUC_{idarubicinol}/AUC_{idarubicin}$ of 3.8 over the first 24 hr.

Gams & Gerber (1990) – FCE report IMI 30/615i

Twenty nine (29) patients entered the study; PK was measured in 13 of these (4 solid tumors, 9 leukemia) at doses ranging from 30 to 150 mg/m^2. Idarubicin was given in 3 day cycles followed by 21 days off treatment. Samples were obtained for PK on Day 1 at 0 (pre-dose), 5, 10, 30, 60, 120, 240, 480 min after dosing, on Day 2 at 0, 2, 4, and 8 min after dosing, on Day 3 at 0, 2, 4, 8 hr after dosing, on Days 4, 5, 6, and 7 at 72, 96, 120 and 144 hr. Results indicated considerable intersubject variability in PK, and data was considered insufficient to relate C_{max} and AUC to hematologic effect.

Tan et al (1987)

Forty-two (42) evaluable children 1-19 years old were enrolled. Twenty-seven (27) had leukemia and 15 had various solid tumors. The drug was administered IV in escalating doses of 10 to 40 mg/m^2/course in 3 equal fractions over 3 consecutive days at 14- to 21-day intervals. Pharmacokinetics were measured in 7 patients receiving from 15 to 40 mg/m^2/course of treatment. In most patients, the plasma clearance of idarubicin fit a 3 compartment model with a harmonic mean half-life of 2.4 min, 0.6 h, and 11.3 h for the α, β, and γ elimination phases, respectively. The median terminal half life of idarubicin was 8.5 hr (range: 3.6 - 26.4 hr). Idarubicinol was the only metabolite detected in the plasma and it accumulated during the 3 days of therapy and it exhibited a median half life of 43.7 hr (range: 27.8 - 131 hr).

Other Pertinent Pharmacokinetic Information from the Literature

Goebel (1993) conducted a literature review of oral idarubicin, the first oral anthracycline with potent antitumor activity. The article discusses the PK activity of oral idarubicin in adults and children and shows that its lipophilicity is increased compared with other anthracyclines. In addition, idarubicinol, the principal metabolite, is produced in high concentrations and had potent antitumor activity. Consequently, both idarubicin and idarubicinol partition readily into the cerebrospinal fluid (CSF). Preclinical and clinical experiences with oral idarubicin were reviewed and show that oral idarubicin has a mean bioavailability of 30% and has demonstrated efficacy in several malignant diseases, including ALL and AML. The incidence of the most common adverse events (AEs), nausea, vomiting, diarrhea, and mucositis, is higher after oral than after IV idarubicin. There is a somewhat higher rate of AEs related to the liver, resembling intrahepatic cholestasis, possibly due to a first-pass effect. In addition, oral idarubicin, which has been studied with cumulative doses of □360 mg/m^2 (and up to 600 mg/m^2 in one study), has less cardiotoxicity compared with other anthracyclines and compared with IV idarubicin.

Berman (1983) et al report the results of a phase I PK study that included 23 patients, aged 34 to 71 years with a variety of tumor types who received IV idarubicin and 32 patients, aged 31 to 75 years with a variety of tumor types who received oral idarubicin. Initial dose of IV idarubicin was 5 mg/m^2 and initial dose of oral idarubicin was 10 5 mg/m^2 - The publication itself states: “The initial p.o. dose of 4-DMDR was 10 mg/sq m and was given every21 days.”; see http://cancerres.aacrjournals.org/content/43/12_Part_1/6096.full.pdf - . The plasma-concentration time curves for IV idarubicin were triphasic and similar to those seen with doxorubicin. There was a metabolite, 4-DMDR-ol after both IV and oral administration. Significantly more AEs of nausea and vomiting were reported for patients given oral idarubicin compared with those given IV idarubicin. Myelosupression and alopecia were also reported. The nonhematological toxicity observed in this study was less than that reported for doxorubicin and daunorubicin.

Camaggi (1992) et al report the results of a phase I study crossover study evaluated the PK and metabolism of 21 patients with advanced cancer. The IV dose of idarubicin was 12 mg/m^2 and the oral dose of idarubicin was 30 to 35 mg/m^2. The patients were in 4 groups: patients with normal hepatic and renal function, patients with liver metastasis and normal renal function, patients with renal dysfunction, and patients with hepatic and renal dysfunction. It was determined that idarubicin PK was related to the integrity of renal function. The terminal $t_{1/2}$ and mean residence time of the active metabolite (idarubicinol) were significantly increased in the renal-impaired patients. In the patients who received oral idarubicin, a biphasic decay pattern was noted. The AUC of idarubicinol was greater after oral administration that after IV treatment in proportion to the AUC of idarubicin. Patients with both hepatic and renal impairment had significantly reduced bioavailability of idarubicin (15.7% ± 5.2%) for both the IV and oral treatment compared with the other patients (25.2% to 35.7%). More patients who received IV idarubicin developed leucopenia that patients who received oral idarubicin (p=0.041), and more patients who received IV idarubicin developed anemia than patients who received oral idarubicin, though the difference was not statistically significant. More patients who received IV idarubicin experienced nausea and vomiting than patients who received oral idarubicin (p=0.015).

Paediatric PK Conclusions

On the basis of the results reported in these 4 studies, the MAH proposes to include the following text in Section 5.2 of the idarubicin European Union (EU) Summary of Product Characteristics (SmPC):

Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2/3 day course of treatment, showed a median idarubicin half life of 8.5 hr (range: 3.6 – 26.4 hr). The active metabolite, idarubicinol, accumulated during the 3 day therapy, exhibiting a median half life of 43.7 hr (range: 27.8-131 hr). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2/3 day course of treatment, showed a median terminal half life of idarubicin of 9.2 hr (range: 6.4-25.5 hr). Significant accumulation of idarubicinol was seen over the 3 day treatment period.

Assessor's comment

The paediatric PK conclusion as well as the text proposed for sec. 5.2 of the SmPC is identical with the original submission (see page 33, PK Conclusions).

The proposed text as such contains a mistake requiring a clarification as follows: It is understood that the text proposed for the paediatric patients treated with iv idarubicin derives from study Tan et al (1987) - CANCER RESEARCH 47: 2990-95, 1987; see e.g. http://cancerres.aacrjournals.org/content/47/11/2990.full.pdf - whereas the PK data after oral administration are those published by Pui et al (1988) - CANCER RESEARCH 48: 5348-52, 1988; see http://hwmaint.cancerres.aacrjournals.org/cgi/reprint/48/18/5348- . Seemingly the dose range investigated after iv ("*15 to 40 mg/m^2/3 day course")* and oral ("*30 to 50 mg/m^2/3 day course"*) administration were approximately the same. In fact they were not:
The daily dose in the Tan study was 5-13.3 mg/m^2 per day (see table 1 above, the wording of the publication [*"The drug was administered in escalating doses of 10 to 40 mg/m^2/course in 3 equal fractions over 3 consecutive days…"*] as well as table 5 of the publication) whereas the daily dose, which was administered repeatedly on 3 consecutive days was actually 30 to 50 mg/m^2 per day in study Pui et al (see wording of the publication; *"Fifteen children with acute leukemia in relapse, refractory to conventional therapy, were treated with idarubicin administered*

orally for 3 consecutive days in dosages ranging from 30 to 50 mg/m^2 per day at 19-to 21-day intervals.").
As for the PK data (except data on accumulation) the single dose is relevant, the text should be revised so that it refers not on the dose of the overall 3 days course but reports the daily dose.

As to the actual answers to question # 1 themselves it is a little bit difficult to extract them from the display of the MAH:
It is understood that differences in-between paediatric and adult PK data are seen by the MAH as follows. *"Despite variability in pharmacokinetic parameters between patients and studies and relatively small number of subjects evaluated, the majority of studies provided similar overall findings, although data suggests total body clearance may be lower in the paediatric population than in the adult population."* However, at another place a further difference is reported ("*In adults, the reported mean elimination half-life for idarubicin (range 12-34.8 hours) is longer than that reported in the paediatric population (range 9.2-17.6 hours).*"). As a decreased clearance (e.g. due to hepatic or renal impairment) should usually result in a prolonged terminal half-life, the pattern decreased Cl_{tb} and shortened $t_{1/2}$ for idarubicin in children could mean that children half a considerably larger Vd - T1/2 ~ (0.693)*V/Cl, see http://tpx.sagepub.com/content/23/2/115.full.pdf - than adults. A larger Vd in children, however, has not been reported (see e.g. the 562 L/m^2 in table 1 above). These observed/reported differences in PK of adults vs. children, thus, need still discussion. The MAH was requested for a discussion of these differences. The discussion, however, is missing.
As to differences of absorption/bioavialabilty of oral idarubicin in adults, children and adolescents it is understood that there are no data available on oral/relative bioavailability of idarubicin in children and adolescents so that no answer to this part of question # 1 can be given.

Question # 2

2. The MAH should provide a literature review comprising also relevant current guidelines for AML in childhood. With this literature review the MAH should discuss the conclusion of the RMS that idarubicin (besides DaunoXome) is the state of the art first line anthracycline to be used in children with AML (at least those with high risk AML).

Response of the MAH

The published literature, as well as the National Comprehensive Cancer Network Guidelines for AML (NCCN 2011**),** supports the use of idarubicin as a first-line agent in the treatment of children with AML or for remission induction in relapsed or refractory patients. Twenty-four (24) publications are summarized below:

Carella et al (1990) reported the results of preclinical and clinical studies using idarubicin in the treatment of acute leukemias. When used as a single agent, idarubicin produced complete remission (CR) in 20% and 30% of patients with heavily pretreated paediatric and adult AML and ALL respectively. Idarubicin combined with cytarabine and/or other antileukemic agents produced CRs in 46% of patients with refractory or relapsed AML and in 58% of patients with refractory or relapsed ALL (adult and paediatric). Subsequently, idarubicin has been employed in untreated AML patients in combination with cytarabine and/or etoposide, producing CRs in more than 80% of patients. In ALL patients the drug has been used in combination with vincristine, cytarabine and prednisone, producing CRs in 82% of patients. Recently, idarubicin has been utilized in combination with intermediate doses of cytarabine in refractory or relapsed ALL and AML, and 70% of patients achieved CR. Preliminary results of ongoing prospective

randomized studies in untreated adult AML seem indicate that idarubicin is at least equivalent, if not superior to daunorubicin. The antileukemic activity of idarubicin given orally as single agent, or in combination with other drugs, has been shown in AML and myelodysplastic syndromes. The toxicity of idarubicin includes mild nausea and vomiting, alopecia and liver dysfunction. Ongoing randomized trials comparing idarubicin to daunorubicin should provide more information about the potential cardiotoxicity of this drug.

Dinndorf et al (1997) report the results of a phase I study (Children's Cancer Group, CCG-0922) to determine a tolerable dose of idarubicin given with fludarabine and cytarabine in children with relapsed or refractory leukemia. The phase I study was extended to a limited phase II study to assess the activity of this combination in children with acute myelogenous leukemia (AML). This was a multi-institutional study within the CCG. Eleven (11) patients were entered onto the phase I study: 7 with AML, 3 with ALL (ALL), and 1 with chronic myelogenous leukemia (CML). The maximum tolerated dose (MTD) of fludarabine and cytarabine determined in a previous study was a fludarabine loading dose (LD) of 10.5 mg/m^2 followed by a continuous infusion (CI) of 30.5 mg/m^2/24 hours for 48 hours, followed by cytarabine LD 390 mg/m^2, then CI 101 mg/m^2/h for 72 hours. Idarubicin was given at 3 dose levels: 6, 9, and 12 mg/m^2 intravenously (I.V.) on days 0, 1, and 2. The phase II portion of the trial included 10 additional patients with relapsed or refractory AML. Results: A dose of idarubicin 12 mg/m^2/d for 3 days given in combination with fludarabine and cytarabine was tolerated. The major toxicity encountered was hematologic. Nonhematologic toxicities included transaminase elevations, hyperbilirubinemia, and infections. Eight (8) of 10 patients with AML in the phase II portion (12 mg/m^2 idarubicin) achieved a CR. Conclusion: This combination is active in patients with relapsed or refractory AML. The major toxicity encountered is hematologic. This regimen may be useful therapy for AML and should be compared with standard induction therapy in children with newly diagnosed AML.

Leahey et al (1997) report the results of a phase I/II trial of escalating doses of idarubicin (IDA) in conjunction with the previously established MTD of fludarabine/arabinoside (F-ara-A/ara-C) in children with refractory or recurrent AML. This was a phase I/II trial in parallel with CCG study 0922, which involved dose escalation of Ida at levels of 6 mg/m^2, 9 mg/m^2, and 12 mg/m^2 over 15 minutes on days 0, 1, and 2. As phase I safety was documented by CCG, the dose of Ida given was increased on days 0, 1, and 2 of the F-ara-A/ ara-C infusion (F-ara-A: 10.5 mg/m^2 over 15 minutes and 1.27 mg/m^2/hour for 48 hours followed by ara-C: 390 mg/m^2 over 15 minutes and 101 mg/m^2/hour for 72 hours). Ten (10) of 15 patients achieved remission. There was 1 toxic death due to adult respiratory distress syndrome. The median time to an absolute neutrophil count (ANC) > 200/µL was 29 days; ANC > 1,000/µL was 41 days; and platelets > 100,000/µL was 45 days. Conclusions: A dose of 12 mg/m^2/day × 3 of Ida did not exceed dose-limiting toxicity with this combination of F-ara-A/ara-C. Substantial activity of this regimen was seen in paediatric patients with AML.

Fleischhack et al (1998) report the results of a phase II trial to explore the potential feasibility and efficacy of a reinduction therapy consisting of fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor (G-CSF) for AML patients with poor prognosis. Twentythree (23) patients aged 1.2-17.5 years with refractory (n=3) relapsed (n=19) or secondary (n=1) AML were treated with the IDA-FLAG regimen, a combination therapy of idarubicin (days 2-4, 12 mg/m^2/d), fludarabine (days 1-4. 30 mg/m^2/d), cytarabine (days 1-4, 2000 mg/ m^2/d) and G-CSF (day 0 up to ANC >1×109/1, 400 µg/m2/ d). They received a total of 37 courses of IDA-FLAG and/or FLAG (IDA-FLAG without idarubicin). 17/23 patients achieved a CR with a median duration of 13.5 months (1- 39 months), 1 patient showed a partial remission, and 5 were nonresponders while in CR. Eleven (11) patients underwent bone marrow or peripheral blood stem cells (PBSC) transplantation. Overall, 9 patients remained in continuous CR with a median duration of 17.5 months (9.5 - 39 months). The toxicity of the IDA-FLAG

courses was more severe than for the FLAG courses with marked neutropenia and thrombocytopenia (for IDA-FLAG: median 22.5 and 25 d respectively; for FLAG: median 10.5 and 14d respectively).
Pulmonary infections were the main nonhaematological toxicity. One (1) patient died in CR from invasive aspergillosis. The IDA-FLAG regimen produced a CR of >12 months in more than half of the patients and can be recommended as a therapeutic option prior to allogeneic or autologous bone marrow transplantation.

Creutzig et al (2001) report a randomized trial (AML-BFM 93) in which they compared 60 mg/m^2/day daunorubicin with 12 mg/m^2/day idarubicin for 3 days each, combined with cytarabine and etoposide during induction. Results showed a significantly better blast cell reduction in the bone marrow on day 15 in patients of the idarubicin arm (25 of 144 = 17% of patients with 5% blasts compared to 46 of 149 = 31% of patients after daunorubicin, P_X^2 =0.01).
This was, however, mainly seen in high risk patients treated with idarubicin (19% vs 38%, P_X^2 = 0.007). A similar rate of cardiotoxicity, World Health Organisation (WHO) grade 1-3 shortening fraction reduction after induction occurred in 6% patients in both arms. Bone marrow toxicity differed slightly with a median recovery time of neutrophils >500/L of 25 days (daunorubicin) compared to 27 days (idarubicin), *P* = 0.05. In the total group of patients probabilities of 5 years event-free survival (EFS) and disease-free survival (DFS) were similar for patients treated with daunorubicin or idarubicin (49% ± 4% vs 55% ± 4% and 57% ± 4% vs 64% ± 4%, P logrank 0.29 and 0.15, respectively). However, in patients presenting with more than 5% blasts on day 15 there was a trend for a better outcome after treatment with idarubicin (*P* logrank 0.06). Together with the early effect seen for high risk patients these results indicate a better efficacy of idarubicin than of daunorubicin during induction with a similar rate of toxicity.

O'Brien et al (2002) report the results of consecutive clinical trials in children with newly diagnosed AML in which daunorubicin (group 1, n = 102) or idarubicin (group 2, n = 160) was used during the remission-induction (RI) and the early consolidation phases of chemotherapy. Idarubicin was given at a dose of either 10 mg/m^2 (group 2A, n=106) or 12 mg/m^2 (group 2B, n=53). A high rate of RI was achieved for all groups (95% group 1, 90% group 2A, 94% group 2B). There were no significant differences in 5-year EFS or in overall survival (OS) when the 3 groups were compared (group 1: EFS 50%, OS 56%; group 2A: EFS 50%, OS 60%; group 2B:-EFS 34%, OS 50%). RI deaths resulting from treatment toxicity were low—2% for group 1 and 5% for group 2. More gastrointestinal, pulmonary, and renal toxicity, but fewer infections, were observed in patients receiving idarubicin (P<0.001, P = 0.04, P = 0.03, respectively). Following RI chemotherapy, all patients received 3 to 4 more courses of identical chemotherapy and then underwent either autologous (n = 156) or an allogeneic bone marrow transplant (BMT) (n = 35). OS was higher in allogeneic BMT patients than in autologous BMT patients (79% vs 63%;P = 0.23). It was concluded that daunorubicin is as effective as idarubicin for remission-induction therapy for childhood AML and has reduced toxicity.

Lange et al (2004) – report the results of Children's Cancer Group Pilot Study CCG-2941, a study that assessed the toxicity and feasibility of substituting 4 mg of daunorubicin (DNR) with 1 mg of IDA in intensive-timing daunorubicin-based induction therapy (DNR/DNR) used in CCG-2891. On days 1 through 3 and 10 through 14, patients received 2 courses of dexamethasone, cytarabine, 6-thioguanine, etoposide, and IDA (IDA/IDA). After enrollment of 65 patients, toxicity prompted replacement of IDA with DNR (IDA/DNR) on days 10 through 14 for the remaining 28 patients. Outcomes were compared with those of intensive timing in CCG-2891. Results: Treatment-related mortality (TRM) after 2 courses of induction was not significantly different among the 3 regimens: 14% with IDA/IDA, 7% with IDA/DNR, and 9% with DNR/DNR. In course 1 of CCG-2941 IDA/IDA, 11% of patients withdrew compared with 1.5% in CCG-2891 (P < 0.001) and 5% in CCG-2941 IDA/DNR (P = not significant). Compared with CCG-2891 DNR/DRN, CCG-2941 IDA/IDA increased days in hospital (43 vs 36 days; P = 0.007), mean

duration of course 1 by a week (P = 0.002), and risk of grade 3 or 4 hyperbilirubinemia (18% v 5%; P = .02). Toxicity of IDA/DNR was not different from that of DNR/DNR in CCG-2891. The mean day 7 marrow blast percentage was 11.4% in CCG-2941 vs 21.1% in CCG-2891 (P = 0.004). Remission induction, survival, and EFS rates were not significantly different from those of CCG-2891. Conclusion: In CCG-2941, excessive toxicity and withdrawals outweighed potential benefits of early response with IDA.

Dluzniewska et al (2005) report the results of a new treatment protocol for AML employing idarubicin in place of daunorubicin that was introduced in 1998 and that produced better initial responses, an increase in the number of patients attaining remission after induction therapy and a proportional increase in standard-risk patients. The probability of 5-year event-free survival (pEFS) for the whole group of patients increased from 36 to 47%. In standard- and high-risk groups, the 5-year pEFS was 62 and 33%, respectively. The probability of 5-year DFS was 58% in the whole group, and there were no differences between risk groups. Unsatisfactory treatment results in children classified into the high-risk group are principally due to the low remission rate.

Smith et al (2005) report the results of 3 Phase III prospective clinical trials for children with de novo acute myeloid leukemia conducted by the CCG between the years 1979 and 1995. A total of 1903 eligible children ages birth to 21 years of age were enrolled on CCG 251 (n=485), CCG 213 (n=532) and CCG 2891 (n=886). Follow-up was ongoing as of 2005, with medians of 7.9, 10.9 and 8.6 years, respectively. These 3 clinical trials developed dose- and time-intensive induction regimens based upon high-dose cytarabine and daunomycin and randomly assigned patients to allogeneic bone marrow transplantation in first remission if an human lymphocyte antigen (HLA)-matched related donor was identified. Despite dose- and time-intensive induction regimens, remission induction rates remained relatively stable at 77-78%. However, OS, EFS, and DFS increased for patients receiving intensive-timing induction therapy in comparison to patients who received standard-timing induction, regardless of the type of postremission therapy. Outcomes were best for patients receiving intensive-timing induction followed by matched related donor allogeneic transplantation with DFS of 65+/-9% at 6 years.
These 3 clinical trials have established a strong foundation for the development of future studies focusing on further risk group stratification and the development of novel, molecularly-targeted therapies.

Creutzig et al (2006) report the results of a study to improve prognosis in children with AML by randomized comparisons of (1) two short consolidation cycles versus the Berlin-Frankfurt-Muenster (BFM)-type biphasic 6-week consolidation and (2) the prophylactic administration of G-CSF versus no G-CSF. Further, therapy for standard risk patients was intensified by addition of a second induction, HAM (high-dose cytarabine and mitoxantrone): A total of 473 patients younger than 18 years with de novo AML were enrolled in trial AML-BFM 98. Patients received 5 courses of intensive chemotherapy, cranial irradiation, and 1-year maintenance therapy. Results: Four hundred eighteen (418, 88%) patients achieved remission. Compared with trial AML-BFM 93, early deaths decreased from 7.4 to 3.2% (P = 0.005), and 5-year overall survival increased from 58% to 62% (log-rank P = 0.03). Both types of consolidation therapy led to similar outcome (EFS, 51% v 50%), but in the 2-cycle arm, treatment duration was shorter (median duration, 15 days), and treatment related mortality was lower (5 vs 9 patients). G-CSF shortened neutropenia, but did not reduce the rate of severe infections. Intensification of induction therapy did not improve prognosis of standard-risk patients (EFS, 62% v 67%). Conclusion: Overall results were improved by neither the administration of G-CSF nor by cycle therapy; however, the latter was easier to perform. Compared with study AML-BFM 93, therapy intensification with HAM in standard-risk patients did not result in improved prognosis. Future treatment designs have to balance intensification of treatment with higher toxicity, improve supportive care, and to consider alternative treatment strategies.

Ganzina et al (1986) report that the anti-leukemic activity of idarubicin is superior to that of DNR or doxorubicin (DX) and is active by both the IV and the oral routes of administration.
After IV and oral administration in humans, idarubicin is rapidly metabolized to daunorubicinol and the plasma levels of this metabolite are consistently higher than those of the unchanged drug.
Idarubicinol has been shown to be as potent and as active as the parent compound. Phase IIclinical trials show that IV idarubicin is a potent antileukemic agent active in relapsed or refractory AML and ALL (adult and paediatric) either as single agent or in combination with Ara-C at doses of 8-12 mg/m^2 by IV day 1, 2 and 3 or 7-8 mg/m^2 IV daily x 5 days (adults).
There is evidence of lack of cross-resistance with parent drugs and other antileukemic agents.
Phase III studies in previously untreated acute leukemias have been initiated. Oral idarubicin has antitumor activity in breast cancer at the doses of 35-45 mg/m2 q 3-4 weeks or 15 mg/m^2 daily x 3 days q 3-4 weeks. Idarubicin has activity as a single agent in adult leukemias at the doses of 20-30 mg/m^2/day X 3 days. The safety of administration (no risk of extravasation), the good tolerability, and the reduced potential for cardiotoxicity, make oral idarubicin particularly attractive for further clinical development. Whether idarubicin proves to be more effective and/or less cardiotoxic in clinical therapy than DNR or DX remains to be seen through prospective randomized studies which have been already initiated both in leukemias and solid tumors.

Lowenthal et al (1987) report that oral idarubicin was given as single-agent treatment for AML in 18 poor-risk patients. They comprised 9 previously untreated elderly patients, aged 69 to 86 years, and 9 relapsed pretreated patients, aged 41 to 76 years. Overall, 2 patients achieved CR (including 1 with preceding refractory anemia with excess of blasts) and 7 achieved partial responses. Dose-limiting toxic effects were diarrhea and sepsis. In this limited study, oral idarubicin at a dose of 20-25 mg/m^2/day x 3 was well-tolerated with potent antileukemic effects. The oral formulation deserves more widespread evaluation.

Harousseau et al (1989) report that oral IDR was given at a dose of 30 mg/m2 daily for 3 d in 20 patients aged 65 to 79 years with previously untreated AML. Five (5) patients whose marrow remained blastic at d 14 received a second course; 8 patients achieved CR (6 after 1 single course). There were: 1 early death, 4 deaths in aplasia, 7 failures. The hematologic toxicity was high. All but 1 patient had to stay in hospital and the duration of neutropenia was 12 to 34 days (median 19). Oral idarubicin is an effective therapy for AML in elderly patients but the total dose of 90 mg/m^2 is too aggressive to be administered safely outside the hospital.

Malik (1989) report 14 patients with poor-risk acute AML and 5 patients with accelerated phase/blast crisis chronic myeloid leukaemia (CML) were treated with 3 days with oral idarubicin (25 mg/m^2/day). No CRs or return to chronic-phase CML were observed. A fall in the peripheral blast count was seen in all patients with the first cycle of treatment, and with subsequent cycles in CML patients, but all responses were transient, with eventual reemergence of peripheral blasts. In some patients, there was a clear cut improvement in symptoms such as bone and splenic pain. Five (5) of the AML patients and all of the CML patients were treated as out-patients. In this group of patients oral idarubicin was found to be a useful drug for palliative treatment.

Lange et al (2008) report the results of a phase 3 trial (CCG-2961) that incorporated 3 new agents, idarubicin, fludarabine and interleukin-2, into an AML protocol using intensive-timing remission induction/consolidation and related donor marrow transplantation or high-dose cytarabine intensification. Among 901 patients under age 21 years, the 5-year survival was 52%, and the EFS rate was 42%. Survival improved from 44% between 1996 and 1998 to 58% between 2000 and 2002 (P = 0.005), and TRM declined from 19% to 12% (P = 0.025). Partial replacement of daunomycin with idarubicin in the 5-drug induction combination achieved a remission rate of 88%, similar to historical controls. Postremission survival was 56% in patients

randomized to either 5-drug reinduction or fludarabine/cytarabine/idarubicin. For patients with or without a related donor, respective 5-year DFS was 61% and 50% (P = .021); respective survival was 68% and 62% (P = .425). Donor availability conferred no benefit on those with inv(16) or t(8;21) cytogenetics. After cytarabine intensification, patients randomized to interleukin-2 or none experienced similar outcomes. Factors predictive of inferior survival were age more than 16 years, nonwhite ethnicity, absence of related donor, obesity, white blood cell (WBC) count more than 100,000 × 10^9/L, −7/7q−, −5/5q−, and/or complex karyotype. No new agent improved outcomes; experience may have contributed to better results in time.

Rubnitz et al (2008) reviewed currently available treatments for AML and noted that idarubicin is commonly used as part of a multidrug regimen with cytarabine and etoposide because in vitro and preclinical studies suggest that it offers a greater clinical benefit due to its faster cellular uptake, increased retention, and lower susceptibility to multidrug resistant glycoprotein. In addition, idarubicinol, the active metabolite, has a prolonged plasma half-life (54 hours) and has antileukemic activity in the cerebrospinal fluid.

Shah and Agarwal (2008) reviewed the recent advances in the management of AML and noted that idarubicin is used commonly because in vitro and preclinical studies suggest that it offers a greater clinical benefit because of its faster cellular uptake, increased retention, and lower susceptibility to multidrug resistant glycoprotein. In addition, its main metabolite, idarubicinol, has a prolonged plasma half-life (54 hours) and has antileukemic activity in the cerebrospinal fluid.

Alnaim (2008) reviewed the scientific literature evaluating the efficacy and tolerability of idarubicin, concluding that idarubicin is an effective alternative for the treatment of different types of AML. It significantly increases response rates and survival time when used in combination with other antileukemic agents. In comparative studies, there was a trend toward the superiority of IDA over daunorubicin. However, these studies are insufficient to recommend IDA as a replacement for daunorubicin, and further studies will be needed to ascertain if statistically significant differences in efficacy exist between the 2 drugs.

Absolon et al (2009) reports the results of a recently completed Phase III clinical trial in children with de novo AML which showed long-term DFS in 50 - 60% of children. This review describes the contributions from early intensification of therapy and postremission intensification using highly myelosuppressive chemotherapy strategies and discusses the controversial roles of allogeneic bone marrow transplantation, maintenance therapy and central nervous system (CNS) irradiation. The article concludes that current strategies focusing on the identification of critical biologic features and measurements of early response to therapy allow for greatly improved risk group stratification. Future improvements in the treatment of children with AML will depend on a better understanding of the biology of the disease, targeted therapeutic approaches directed to specific biologic targets, selective use of allogeneic transplantation and innovative clinical trial designs that will allow for the testing of an increasing number of new agents in increasingly small numbers of patients in defined risk groups.

Lee et al (2010) investigated the outcome of idarubicin plus N4-behenoyl-1-β-Darabinofuranosyl cytosine (BHAC)-based chemotherapy (BHAC group, n=149) compared to idarubicin plus cytarabine-based chemotherapy (cytarabine group, n=191) for childhood acute myeloid leukemia (AML). Between January 1996 and December 2005, 340 children with AML from 5 university hospitals in Korea received the BHAC-based or cytarabine-based chemotherapy, with or without hematopoietic stem cell transplantation. After induction therapy, 264 (77.6%) of 340 children achieved a CR (CR) and 43 (12%) achieved a partial remission (PR). The CR rate in the BHAC group was higher than in the cytarabine group (85.2% vs. 71.7%, P=0.004). However, the overall response rate (CR+PR) was not different between the two groups (93.3% vs. 87.9%,

P=0.139). The 5-yr estimates of OS of children in the two groups were similar (54.9% for the BHAC group vs. 52.4% for the cytarabine group, P=0.281).
Although the results were analyzed according to the treatment type and cytogenetic risk, the OS showed no significant difference between the BHAC group and the cytarabine group. In the present study, the clinical outcomes of the BHAC-based chemotherapy, consisting of BHAC, idarubicin, and 6-TG, are comparable to that of the cytarabine-based chemotherapy for childhood AML.

Abrahamsson et al (2010) reports results from the Nordic Society for Paediatric Hematology and Oncology (NOPHO)-AML 2004 study, 1 of a series of consecutive population-based paediatric AML treatment studies conducted in all 5 Nordic countries. All patients younger than 15 years of age were treated with a course of idarubicin, cytarabine, etoposide, and 6-thioguanin. Those with a good response were allowed to attain hemotologic recovery before the second 14.9% blasts) were recommended immediately for therapy. Patients who did not attain remission after the second course received fludarabine, cytarabine, and granulocyte colonystimulating factor. Poor responders received allogenic, stem-cell transplantation (SCT) as consolidation. Seventy-four percent (74%) of patients had a good response, 17% had an intermediate response, and 7% had a poor response after the first course. The overall remission frequency was 97.4%, with 92% in remission after the second course. The rate of induction death was 1.3%. Patients with an intermediate response had a lower EFS (35%) compared with those whose response was good (61%) and those whose response was poor (82%).

Conclusion: The NOPHO-AML 2004 induction strategy gives an excellent remission rate with low toxic mortality in an established population. Outcome is worse in patients with intermediate response but may be improved by intensifying consolidation in this group using SCT.

Bayram et al (2010) reports the results of a study to compare the effects of 2 different dosages of idarubicin (12 mg/m^2 versus 8 mg/m^2) therapy for newly diagnosed AML patients. Sixty eight (68) patients with AML were treated between February, 1998 and January, 2005. When oral nutrition was interrupted, parenteral nutrition was given. OS, EFS, and DFS data were assessed and other tests were performed when needed. There were 26 patients (38.2%) in group 1 and 42 patients (61.8%) in group II. Result: After the first induction therapy, 20 patients (76.9%) in group 1 and 36 in group II (85.7%) had CR or partial remission. After 2 courses of induction, TRM was 34.6% in group I and 7.1% in group 2 (p: 0.006). OS of the patients in group 1/2 were 44/81% for 12 months, 34/54% for 24 months, 29/48% for 36 months. EFS were 43/65% for 12 months, 34/50% for 24 months, and 29/50% for 36 months. OS and DFS rates were statistically significant but EFS rates were not, in groups 1 and 2. Conclusion: The protocol with idarubicin dose of 8 mg/m^2/day has less TRM.

National Cancer Institute (2011) reports that the anthracycline that has been most used in induction regimens for children with AML is daunorubicin, though idarubicin and the anthracenedione mitoxantrone have also been used. A randomized study (Creutzig et al (2001) in children with newly diagnosed AML comparing daunorubicin with idarubicin (each given with cytarabine and etoposide) observed a trend favoring idarubicin in terms of remission rate, but use of idarubicin did not produce significant improvements in either EFS or OS.

The National Comprehensive Cancer Network Guidelines for AML (2011) contains a recommend dose regime for paediatric patients for idarubicin as first-line treatment: standarddose cytarabine 100-200 mg/m^2 continuous infusion for 7 days with idarubicin 12 mg/m^2 or daunorubicin 60-90 mg/m^2 for 3 days; or high-dose cytarabine 2-3 g/m^2 every 12 hours for 3 days with idarubicin 12 mg/m^2 or daunorubicin 45-60 mg/m^2 for 3 days (1 cycle) (category 2B).

CONCLUSION

The use of idarubicin as a first-line agent in the treatment of children with AML or for remission induction in relapsed or refractory paediatric patients is well supported by the published literature and recommended by the National Comprehensive Cancer Network Guidelines for AML (NCCN 2011**)**.

Assessor's comment

The MAH provided the literature review requested comprising also treatment guidelines for childhood AML.

For means of clarification, however, it has to be stated that it is considered unlikely that the NCCN Guidelines for AML comprised in 2011 a *"recommend dose regime for paediatric patients for idarubicin as first-line treatment"*. Rather, NCCN Clinical Practice Guidelines in Oncology, AML, version 2.2013 - See http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (last visit 10.03.2013) - states (p. MS-2): *"The AML Panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) convenes annually to update guidelines for the diagnosis and treatment of AML **in adults**."* A same statement can be found in the 2011 Guidelines - J Natl Compr Canc Netw 9: 280-317, 2011; see also http://www.jnccn.org/content/9/3/280.full.pdf - so that the assessor considers that NCCN Guidelines for AML are guidelines for adult but not childhood AML.

Overall, however, the literature review presented - albeit not all publications clearly refer to idarubicin, or do not allow the assessment of efficacy and safety of idarubicin in childhood AML – confirms that Idarubicin has a long and well established use in childhood AML which currently continues.

The assessor, however, is of the opinion that confirmation of an established use as such does not allow to grant a new indication as the scope of an Article 45 procedure is to assess (still not assessed) studies (available to the MAH) but not publications.

However, this time the literature review presented by the MAH compromises also the publication of the Nordic Society for Pediatric Hematology and Oncology (NOPHO) AML 2004 protocol ("Abrahamsson et al (2010)" - doi: 10.1200/JCO.2010.30.6829; see also http://jco.ascopubs.org/content/29/3/310.full.pdf -) originally discussed by CMS SE, as well as results of studies AML-Berlin-Frankfurt-Münster (BFM) 93 ("Creutzig et al (2001)" - Journal of Clinical Oncology 19: 2705-13, 2001; see also http://jco.ascopubs.org/content/19/10/2705.full.pdf) and AML-BFM 98 ("Creutzig et al (2006)" - doi: 10.1200/JCO.2006.06.5037; see also http://jco.ascopubs.org/content/24/27/4499.full.pdf) to which the RMS DE originally pointed to. Lacking is, however, still result of AML-BFM 2004 - http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/181 (comparing idarubicin and liposomal daunorubicin for remission induction) already mentioned previously by the RMS.

Rather, the sequence of 3 (published) trials using in principle for a decade iv (12 mg/m^2 daily on 3 days) idarubicin as part of the standard induction regimen in childhood AML by the BFM study group – a group well known for its impact on the treatment of leukemias in general in Europe, accompanied by similar trends in the NOPHO preferring idarubicin in place of daunorubicin – seems to justify granting a new indication to iv idarubicin for remission induction in patients previously untreated for childhood AML within the EU.

There is, however, still and obstacle to such a recommendation which are the following design considerations, and conclusion, of the (abstract of the) AML-BFM 2004 - http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;116/21/181 study:

"Improvement of prognosis was attempted by intensification of chemotherapy: (1) Randomized introduction of liposomal daunorubicin (L-DNR) in a higher equivalent dose than idarubicin during induction in both risk groups (L-DNR 80mg/m^2/day/3x) in comparison to standard induction using idarubicin 12mg/m^2/day/3x, each combined with cytarabine and etoposide (L-DNR may offer an increased therapeutic window due to lower cardiotoxicity) and (2) randomised introduction of 2-chloro-2-deoxyadenosine (2-CDA, 2x6mg/m^2) as intensification during the cytarabine/idarubicin (AI) consolidation in HR patients only. … **In conclusion**, … Given the reduced toxicity of L-DNR and a trend towards better survival rates by adding L-DNR during induction and 2-CDA during HR consolidation, these agents will be further used in the forthcoming AML-BFM study.

In this context the conclusion of the publication of the Cukurova University Medical Faculty, Division of Pediatric Oncology, Adana, Turkey (publication **Bayram et al (2010)** - Eur J Gen Med 7: 282-87, 2010; see also http://www.ejgm.org/upload/sayi/11/EJGM-139.pdf in the publication review of the MAH above) is remarkable:

"The protocol with idarubicin dose of 8 mg/m^2/day has less treatment-related-mortality in comparison to that of 12 mg/m^2/day and has better overall survival and event free survival."

In this overall context most recently (Creutzig et al. 2012 on behalf of the AML Committee of the International BFM Study Group) published recommendations from an international expert panel - doi:10.1182/blood-2012-03-362608; see also http://bloodjournal.hematologylibrary.org/content/120/16/3187.full.pdf:

*"**Recommendation: … Induction:** One or 2 courses of induction therapy are routinely used in children and adults. Standard induction therapy comprises 3 days of an anthracycline (eg, daunorubicin at least 60 mg/m^2, **idarubicin 10-12 mg/m^2**, or the anthracenedione mitoxantrone 10-12 mg/m^2) and 7-10 days of cytarabine (100-200 mg/m^2 continuously or twice daily intravenously; ie, "3+7" or "3+10"). With these regimens, > 85% of children and adolescents achieve complete remission (CR). Although a third drug, such as etoposide or 6-thioguanine, is commonly included in induction, their benefit has not been proven."*

Based primarily on the sequence of the 3 BFM trials (AML BFM 93, 98, and 2004), the published standard induction treatment used by NOPHO, and on additional information, considerations and recommendations not compromised in the literature review offered by the MAH, the RMS is of the opinion that currently an indication for iv idarubicin in remission induction in previously untreated patients with childhood AML can be granted in the EU. There is a more recent trend towards a slightly reduced single iv dose compared to the standard dose of 12 mg/m^2/day (x 3 days) based primarily on a potentially better safety profile with lowered treatment related mortality. This may be handled best by recommending a dosage range within the SmPC.

Question # 3

3. The MAH should propose a first line indication in AML of childhood.

Response of the MAH (abridged)

In addition to the literature review, 9 clinical studies/reports were identified as relevant to the idarubicin paediatric assessment. These studies are summarized below. Of note, several studies

(IMI 30/762i, IMI 30/794i, IMI 30/795i) included a limited subset of paediatric patients and Protocol 799-ONC-9041-184 included an unknown number of children; therefore, the relevance of these data to the paediatric population cannot be determined.

Protocol No. 799-ONC-9041-184
Protocol Title: Sub-center report on randomized, open, multi-center, parallel, controlled clinical study comparing the efficacy and safety of idarubicin produced in China to imported idarubicin.

Protocol No. 95-OIDV-090
Protocol Title: Multinational, Multi-Center, Randomized, Active-Controlled, Open-Label Study for the Treatment of Acute Myeloblastic Leukemia in Treatment-Naive Children

Protocol No. IMI 30/762i
Protocol Title: A phase III trial comparing daunorubicin or idarubicin combined with cytosine arabinoside in acute myelogenous leukemia (AML)

Protocol No. IMI 30/615i / Study No. 083F03
Protocol Title: 4-Demethoxydaunorubicin (4DMDR) in Children with Advanced Malignancies: Phase I Study or Oral 4 DMDR and the Clinical Pharmacology of Oral Administration

Protocol No. IMI 30/794i / Study No. ZA 87602
Protocol Title: Combination chemotherapy with arabinosylcytosine (ARA-C), 4-demethoxydaunorubicin (4-DMDR) (idarubicin) and etoposide (VP-16) in patients with acute non-lymphocytic leukemia

Protocol No. IMI 30/795i / Study No. DD 84601
Protocol Title: A Phase II Study of Oral Idarubicin in Children with Acute Leukemias: Evaluation of Toxicity and Efficacy

Protocol No. IMI 30/796i / Study No. ZA 84601
Protocol Title: Oral idarubicin in combination with cytosine-arabinoside in previously untreated patients with acute non-lymphocytic leukemia

Protocol No. IMI 30/799941i / Study No. 073023
Protocol Title: Determination of dose of idarubicin in combination with verapamil for remission reinduction in ALL after 1st marrow relapse; alternative induction while awaiting results in IDR patients – VPL in combination with daunomycin: a groupwide feasibility study

Progress Report No. IMI 30/746i
Report Title: Progress Report to Adria Laboratories on Pediatric Idarubicin Studies

Efficacy Conclusion

The MAH identified the relevant studies/reports to support the paediatric assessment. The data on file for paediatric patients is limited, and includes several studies of the oral formulation. Oral single-agent idarubicin (20 to 25 mg/m^2/day for 3 days has demonstrated efficacy in AML (and as palliative treatment in patients with CML in accelerated phase or blast crisis (Ganzina 1986, Harousseau 1989, Lowenthal 1987, and Malik 1989). Several direct comparisons between idarubicin and daunorubicin are described in the published literature and show that idarubicin is, in general, as effective in the treatment of AML as daunorubicin and has a comparable safety profile. The data in the published reports support the efficacy of idarubicin in paediatric patients with AML, and confirms that the use of idarubicin is well established in current paediatric clinical practice. Established dosing regimens generally range from 10 to 12 mg/m^2/day for 3 days.

Assessor's comment

The 9 studies on file have already been assessed (see sec. 2. Clinical study(ies) of this AR), the reason to abridge the response of the MAH.

The efficacy conclusion of the MAH, in particular that the data on file for paediatric patients is limited, is endorsed. As to the oral administration the assessor agree with the statement provided that ~~efficacy~~ would be replaced by the term activity. Activity of oral idarubicin has been demonstrated in childhood AML even in previously treated patients. However, it should be noted that relative bioavailability of idarubicin is unknown in children, the oral dose discussed by the MAH is approximately the double of the iv while in adults the relative/oral bioavailability is about 20 to 30%, that BFM and NOPHO used exclusively idarubicin iv, and that no therapeutic situation is described by the MAH in which iv idarubicin cannot be administered. For means of low variability of PK the assessor is of the opinion that remission induction in previously untreated patients shall be done best via the intravenous route in all instances.

The requested proposal for a first line therapy indication in childhood AML is not contained in the responses but in the newly submitted SmPC and reads:

"Idarubicin is indicated for first-line treatment of children with acute myeloid leukemia (AML) or for remission induction in paediatric patients with relapsed or refractory AML."

The MAH was not asked for an indication for paediatric patients with relapsed or refractory AML, and the assessor is of the opinion that the 9 studies on file are not demonstrating efficacy (but activity only) in these patients. In summary and in conclusion, the RMS makes the following proposal for an indication:

Idarubicin iv is indicated as part of combination treatment for remission induction of previously untreated children with acute myeloid leukemia (AML).

No indications in children should be given to pharmaceutical forms for oral use.

Question # 4

4. The MAH should discuss a potential therapeutic place of oral idarubicin in AML of childhood.

Response of the MAH

Because of its high lipophilicity, idarubicin is suitable for oral administration and was the first anthracycline to be available in an oral dosage form. Oral idarubicin is used in combination regimens involving other antitumor agents. It is available as a hard capsule containing 5, 10, or 25 mg of idarubicin, and it is recommended that the capsules be swallowed whole with water and should not be sucked, bitten, or chewed. The recommended oral dose of idarubicin for treatment of patients with adult AML is 30 mg/m^2 daily for 3 days as a single agent or between 15 and 30 mg/m^2 daily for 3 days in combination with other antileukemic agents.

The therapeutic place for oral idarubicin is mainly driven by its favourable oral pharmacokinetics and by established safety and efficacy profile in the treatment of haematological malignancies.

Idarubicin is a demthoxylated analogue of daunorubicin. Loss of the methoxyl group confers lipophilicity to the molecule compared to daunorubicin. The solvent / water partition coefficient for idarubicin, daunorubicin and doxorubicin are 13.0, 8.85, and 1.22, respectively. This enhanced lipid solubility of idarubicin relative to other anthracyclines has important implications for its pharmacokinetics.

Following oral administration, idarubicin is rapidly absorbed and plasma concentrations are usually detected in the plasma within 0.5 hours. In contrast, daunorubicin and doxorubicin are not absorbed to any appreciable degree following oral administration. The oral bioavailability of idarubicin varies between patients and studies, but a mean of about 30% is generally observed (Hollingshead 1991, Robert 1993).

Idarubicin is mainly metabolized by reduction of the ketone on C-13 to idarubicinol. The only detectable metabolite, idarubicinol, demonstrates similar in-vitro cytotoxic activity as the parent drug (Hollingshed 1991). Idarubicin metabolism occurs predominantly in the liver; cytochrome P450 enzymes 2D6 and 2C9 have been implicated in the in-vitro metabolism of idarubicin (Colburn 2004). It is noteworthy that formation of the active metabolite is dependent on the route of administration. The metabolite to parent drug ratio is markedly higher after oral compared to intravenous administration of idarubicin. Idarubicinol to idarubicin AUC ratio for oral administration ranged from 2.9 to 18.3 and for intravenous administration ranged from 1.27 to 6.0 (Robert 1993). Plasma concentrations of the metabolite about twice as high after oral as compared to intravenous administration were also noted by other investigators (Smith 1987, Stewart 1991). This is presumably due to the first-pass metabolism of oral idarubicin. Rapid biotransformation of oral idarubicin to idarubicinol accounts for the high total plasma clearance of idarubicin. Following oral administration, the half-life of idarubicin is about 5-24 hours and that for idarubicinol is between 13 and 60 hours.

While the comparative PK of IV and oral idarubicin have been studied extensively in adults, a literature search revealed no comparative PK data for children within the same study.

Pui et al. studied the pharmacokinetics of oral idarubicin in 15 children (10 males) with refractory acute leukemia in haematological relapse. All patients had received prior doxorubicin or daunorubicin. Patient demographics (age, weight) were not provided in the article. Idarubicin was administered orally for three consecutive mornings under fasting conditions. The starting dose was 30 mg/m^2 and dosages were escalated in subsequent patients to 40 and 50 mg/m^2 per day. No dose escalation occurred in the same patient. Pharmacokinetic samples were collected after the first dose at the following times: 0 (predose), 1, 2, 4, 6, 8, 12, and 24 h. PK samples were also collected 24 h after the second and third dose. Concentrations of idarubicin and idarubicinol were measured by high performance liquid chromatography (HPLC) with fluorescence detection. The single dose pharmacokinetic parameters reported by Pui et al are reproduced below in Table 2.

Table 2. Pharmacokinetic Data for Orally Administered Idarubicin During the First 24 Hours after Starting Treatment (n=15) reproduced from Pui et al

	Idarubicin	Idarubicinol
Median $t_{1/2}$ (h)	9.2	Not available
Range	(6.4-25.5)	(11.4-42.4)
Median $C_{max,40mg}$ (ng/mL)	10.6	30.2
Range	2.7-16.7	11.4-42.4
Median t_{max} (h)	6	6
Range	(1-8)	(2-8)
Median AUC_{0-24h} (ng/h/mg idarubicin)	2.4	8.2
Range	(0.7-3.8)	(2.0-14.2)

Median values for $t_{1/2}$, t_{max}, and dose-normalized AUC were determined from all data at all dose levels. For C_{max}, only concentrations at the 40 mg/m^2 dose level are included.
Abbreviations: AUC_{0-24h}=area under the concentration versus time curve, normalized to dose, for 24 h following oral administration; $C_{max\ 40mg}$=peak plasma concentration after an oral dose of 40 mg/m^2;$t_{1/2}$=half life; t_{max}=time to peak concentration after oral administration.
Source: Pui et al (1988)

The authors note that the plasma concentrations of the metabolite exceeded the concentrations of the parent drug at all sampling times. The metabolite to parent drug AUC24 ratio averaged 3.8. This is in contrast to the metabolite/parent drug ratio of 1.9 observed in children given IV idarubicin (Tan 1987). These data suggest that similar to adults, oral idarubicin undergoes first pass metabolism in children which result higher systemic exposure of the active metabolite versus the parent drug.

Pui et al noted in this article that by avoiding high peak plasma concentrations with oral administration it is plausible to decrease not only gastrointestinal toxicity and also cardiac toxicity. As indicated in Table 1 above, the median Cmax following oral idarubicin at the 40 mg/m^2 dose was 10.6 ng/mL (range: 2.7 -16.7). In contrast, Tan et al observed peak plasma concentration of IV idarubicin at 13.3 mg/m^2 doses in excess of 200 ng/mL (based on extrapolation of values reported in their Figure 1) (Tan et al).

While there is insufficient data available from the literature to fully differentiate the PK parameters of adults compared with adolescents and children, it appears that the favourable PK properties of oral idarubicin noted in adults, offer similar advantages for treatment in adolescents, and children.

One (1) phase 1 PK study used oral idarubicin dosages ranging from 30 to 50 mg/m^2 per day at 19-to-21-day intervals in 15 children (n=9 ALL; n=6 AML) with acute leukemia in relapse, refractory to conventional therapy. The authors state that oral idarubicin produced definite antileukemic effects, clearing blast cells from the circulation in 13 children (Pui 1988).

Furthermore, the 2011 National Comprehensive Cancer Network (NCCN) Practice Guidelines for AML include dosing regimens for idarubicin, however, the use of idarubicin in children is not specifically mentioned.

Two (2) phase 1/2 studies have used escalating IV doses of idarubicin (6, 9 and 12mg/m^2) in the management of AML or relapsed AML (Leahey et al, 1997; Dinndorf et al, 1997). Leahey et al evaluated a total of 15 patients between the ages of 1 and 16 and observed a remission rate of 67% (10/15). Dinndorf et al evaluated a total of 21 patients (10 patients with relapsed AML) between the ages of 8 months and 16 years and observed a remission rate of 80% (8/10) in those patients with relapsed AML. Finally, a third phase 2 trial of 23 patients (aged 1.2 to 17.5 years) with refractory (n=3), relapsed (n=19) or secondary (n=1) AML were treated with the

IDAFLAG regimen (intravenous idarubicin 12 mg/m^2/d on days 2 through 4), and 74 % (17/23) of patients achieved CR.

CONCLUSION:

The scientific evidence and the current well established clinical practice support the efficacy of idarubicin in paediatric patients affected by AML and confirm its safe use for this indication.

Assessor's comment

By the comments received by the CMSs it is understood that idarubicin has no MA for oral use in all CMSs involved, a fact which does not preclude recommending addition of paediatric information for existing "oral" SmPCs/PLs in the reminder CMSs.

For this reason, it may be necessary to explain that the MA status of idarubicin iv and oral idarubicin ("Zavedos Oral 5, 10, 25 mg Hartkapseln") differs relevantly in the RMS as follows:

The (oral) indication is limited to attenuated combination remission induction regimens (such as in combination with etoposid, thioguanin) in elderly patients with AML (in accordance with the pivotal trial of the application of idarubicin iv, and the general problem of treatment of AML in elderly patients, idarubicin iv contains a warning for patients older than 65 years of age). Furthermore, in the indication a palliative use is excluded, and it is underlined explicitly that intravenous chemotherapy is the treatment of choice in AML. Accordingly, the recommended oral dose in combination treatment is relatively low (15 to 30mg/m^2 per day (x3)), and a posology for monotherapy is not given.

In front of these backgrounds it becomes not clearer, by the responses of the MAH, and in particular by the conclusion, where the therapeutic place of oral idarubicin is in childhood AML.

Based on the lack of knowledge of relative/oral bioavailability of oral idarubicin in childhood AML, the relative large strength (5mg) of the smallest hard capsules on the market, its complicate instruction for use (*"the capsules be swallowed whole with water and should not be sucked, bitten, or chewed"*), the specifically different indications in adult AML, and the not fully informative response of the MAH to question # 4, **the RMS concludes that currently there is no therapeutic place for idarubicin capsules in childhood AML.**

It is however acknowledged that oral idarubicin is active in childhood AML, has an interesting safety profile (eventually decreased [cumulative anthracycline] cardiotoxicity vs. potentially increased hepatotoxicity), a different parent substance to (active) metabolite ratio.

Question # 5

5. The MAH should submit data confirming a positive benefit-risk ratio of (second line) idarubicin compared to daunorubicin in ALL of childhood. The literature review should be extended. Not only should the efficacy of idarubicin in comparison to other anthracyclines be addressed but also its cardiotoxicity in comparison to other drugs. Moreover, the use of idarubicin in recent clinical trials for children with relapsed ALL should be included in the review.

Response of the MAH (abridged)
In the idarubicin CDS (2008), the indication for second-line treatment of ALL in children is supported by 3 published studies which are summarized below.

Tan et al (1987)
Feig et al (1992)
Feig et al (1996)

Assessor's comment

These three published studies have already been assessed (see Clinical Studies in Published Literature:
so that response of applicant has been abridged. The assessment remains the same that publication **Feig et al (1996)** could allow to amend the indication provided it would be submitted with protocol and CSR. However, the lack of recommendations (in addition to the lacking protocol and CSR for the published study) of idarubicin in treatment guidelines for childhood AML precludes a recommendation for an indication within this procedure.

Other relevant studies from the published literature are discussed and listed in chronological order by year of publication. Publications listed in this section that were not previously submitted are: Carella 1989 - The date of the publication under discussion seems to be actually as of 1990: "Carella A, Berman E, Maraone M, Ganzina F. Idarubicin in the treatment of acute leukemias: an overview of preclinical and clinical studies. Haematologica 1990; 75:159-69, Reid 1990, Giona 1994, Dinndorf 1997, Testi 1997, CALLCG 2009, and Yoon 2009.

Assessor's comment

Since the publications previously submitted were previously displayed and assed in this AR, MAH's responses are abridged in the case the publication is no newly submitted.

Pui et al (1988)

Carella et al (1990) reported the results of preclinical and clinical studies using idarubicin in the treatment of acute leukemias. When used as a single agent, idarubicin produced CR in 20% and 30% of patients with heavily pretreated paediatric and adult AML and ALL respectively. Idarubicin combined with cytarabine and/or other antileukemic agents produced CRs in 46% of patients with refractory or relapsed AML and in 58% of patients with refractory or relapsed ALL (adult and paediatric). Subsequently, idarubicin has been employed in untreated AML patients in combination with cytarabine and/or etoposide, producing CRs in more than 80% of patients. In ALL patients the drug has been used in combination with vincristine, cytarabine and prednisone, producing CRs in 82% of patients. Recently, idarubicin has been utilized in combination with intermediate doses of cytarabine in refractory or relapsed ALL and AML, and 70% of patients achieved CR. Preliminary results of ongoing prospective randomized studies in untreated adult AML seem indicate that idarubicin is at least equivalent, if not superior to daunorubicin. The antileukemic activity of idarubicin given orally as single agent, or in combination with other drugs, has been shown in AML and myelodysplastic syndromes. The toxicity of idarubicin includes mild nausea and vomiting, alopecia and liver dysfunction. Ongoing randomized trials comparing idarubicin to daunorubicin should provide more information about the potential cardiotoxicity of this drug.

Giona et al (1990) reported the results of an Italian cooperative trial using an induction regimen of IDA plus high-dose Ara-C for refractory or relapsed ALL, found an overall 59% CR rate, with 68% CR rate in (21/31) children and 54% in (31/57) adults. The CR rate was significantly affected by WBC count at the beginning of treatment and by the duration of first CR of the patients treated in the first relapse. All of the patients experienced profound myelosuppression.

Nausea and vomiting occurred in 45 patients, 35 patients developed stomatitis which was severe in only one case, 20 patients had diarrhea, and 14 patients showed evidence of hepatic dysfunction, which was reversible in most cases. There were no cases of CHF reported, although all of the patients had previously been treated with anthracyclines. Two (2) patients had reversible arrhythmia and four showed minor electrocardiograph (EKG) changes.
Twenty-one (21) of the 52 patients who achieved CR underwent BMT. Eleven patients relapsed at a median of 4 months (range 1-31) after transplantation, and three patients died while in CR. Seven patients have been in continuous CR for a median of 36 months (range 26-42 months) at the time of the report. Thirty-one patients were not entered into the BMT program, 25 of them due to relapse at a median of 4 months (range 1-25). The authors noted the poor prognosis of patients who received standard maintenance chemotherapy and have devised a different IDA plus Ara-C schedule to minimize toxicity.

Reid et al (1990) report the results of study from the Children's Cancer Study Group to determine plasma PK and CSF concentrations of idarubicin and idarubicinol in paediatric leukemia patients. Based on activity in adults with ALL, the Children's Cancer Study Group initiated studies to evaluate idarubicin in children with leukemia in second or subsequent relapses. As part of those studies, the authors characterized the plasma PK of idarubicin and the major circulating metabolite idarubicinol in 21 patients. Idarubicin plasma elimination was described by a 3-compartment open model following IV infusion (10-15 mg/m^2) on a schedule of weekly for 3 weeks and on a schedule of daily for 3 days every 3 weeks (total dose, 30-45 mg/m^2). There was substantial variability in idarubicin elimination among patients, but no indication of dose-dependent or of schedule-dependent changes in pharmacokinetic parameters.
The mean terminal half-life, total body clearance, and steady state volume of distribution were 17.6 h, 679 mL/min/m^2, and 562 L/m^2, respectively. Idarubicinol elimination was prolonged compared to that of the parent drug with a terminal half-life of 56.8 h. This metabolite clearly accumulated in plasma during the 3 days of treatment on the schedule of daily for 3 days. Urinary recoveries (48 h) of idarubicin and idarubicinol after a single dose of idarubicin were 2.4 and 10.1%, respectively. Idarubicin was detected in 2 of 21 CSF samples obtained 18-30 h after administration. In marked contrast, idarubicinol was detected in 20 of those 21 samples. Concentrations in the 20 samples varied from 0.22-1.05 ng/mL with a mean value of 0.51 ng/mL.

Testi et al (1992)

Giona et al (1994), GIMENA/AIEOP protocol ALL R-87, consisted of an induction phase with IDA plus intermediate-dose cytarabine, followed by a consolidation phase and bone BMT. CR was achieved in 97/147 patients (66%) with a CR rate of 77% in children versus 51% in adults (*P* <0.01). All patients experienced profound myelosuppression and associated infections and hemorrhage. Gastrointestinal toxicity included nausea and vomiting, diarrhea, and mucositis. No CHF or significant arrhythmias were observed; one patient experienced asymptomatic decrease of LVEF to 38% from 64% pretreatment. Forty-eight responders underwent BMT.
Probability of event-free survival $\pm$ standard error (EFS $\pm$ SE was 10.2 $\pm$ 3.1% at 56 months. EFS was 14.3 $\pm$ 4.51% at 56 months for children versus 3.8 $\pm$ 3.41% at 37 months for adults (*P*<0.0001). Among patients treated in first relapse, EFS was 14.2 $\pm$ 7.79% for patients with CR>18 months versus 6.6 $\pm$ 3.17% for those with CR < 18 months (*P* <0.0001). Projected DFS $\pm$ standard error (DFS $\pm$ SE) was 15.4 $\pm$ 4.61% at 55 months for all responders and 43.3 $\pm$ 14.34% at 52 months for allografted patients. Projected overall probability of survival $\pm$ SE was 18.8 $\pm$ 4.13% at 56 months.

Bernstein et al (1997)

Dinndorf et al (1997) report the results of a phase I study (Children's Cancer Group, CCG-0922) to determine a tolerable dose of idarubicin given with fludarabine and cytarabine in children with relapsed or refractory leukemia. The phase I study was extended to a limited phase II study to assess the activity of this combination in children with acute myelogenous leukemia (AML). This was a multi-institutional study within the CCG. Eleven (11) patients were entered onto the phase I study: 7 with AML, 3 with ALL (ALL), and 1 with CML. The MTD of fludarabine and cytarabine determined in a previous study was a fludarabine LD of 10.5 mg/m^2 followed by a continuous infusion (CI) of 30.5 mg/m^2/24 hours for 48 hours, followed by cytarabine LD 390 mg/m^2, then CI 101 mg/m^2/h for 72 hours. Idarubicin was given at 3 dose levels: 6, 9, and 12 mg/m^2 intravenously (I.V.) on days 0, 1, and 2. The phase II portion of the trial included 10 additional patients with relapsed or refractory AML. Results: A dose of idarubicin 12 mg/m^2/d for 3 days given in combination with fludarabine and cytarabine was tolerated. The major toxicity encountered was hematologic. Nonhematologic toxicities included transaminase elevations, hyperbilirubinemia, and infections. Eight (8) of 10 patients with AML in the phase II portion (12 mg/m^2 idarubicin) achieved a CR. Conclusion: This combination is active in patients with relapsed or refractory AML. The major toxicity encountered is hematologic. This regimen may be useful therapy for AML and should be compared with standard induction therapy in children with newly diagnosed AML.

Giona et al (1997)

Neuendank et al (1997)

Testi et al (1997) report the results of a clinical phase II study in previously treated adult patients with AML. A combination of a single high dose (HD) of idarubicin and HD cytosinearabinoside (ARA-C), as designed at the Memorial Sloan Kettering Cancer Center, was administered to 70 adults and children with refractory or early relapse ALL and T-cell lymphoblastic non-Hodgkin's lymphoma (NHL). Therapy consisted of HD-ARA-C 3 g/m^2/d on days 1-5, idarubicin 40 mg/m^2 on day 3, prophylactic intrathecal methotrexate on days 1 and 4, and G-CSF 5 mg/kg/d s.c. from day 7 to hematopoietic reconstitution (PMN > 0.5 x 109/L).
Results: Fifty-five (55) of the 70 patients (78%) achieved CR, 4 died in aplasia due to infection and 11 were non-responders. Recovery of blood counts occurred at a median of 21 days from the start of treatment. Nonhematologic side effects were extremely limited and consisted predominantly of infections. In conclusion, in view of the highly unfavorable series of patients selected, this study confirms the feasibility and antileukemic activity of the HD-idarubicin + HDARA-C combination in patients with refractory and early relapse ALL and NHL. The excellent tolerance to this regimen does not preclude BMT as post-remission treatment.

Giona et al (1998)

Leahey et al (2000)

Childhood Acute Lymphoblastic Leukaemia Collaborative Group (CALLCG) (2009) reported the results of a retrospective analysis that was conducted to assess the beneficial and harmful effects of anthracyclines in the treatment of childhood ALL. Individual patient data from 958 patients in 4 trials recruiting between 1972 and 1984 was collected but only 1 study compared idarubicin to daunorubicin in childhood ALL. No significant differences in any outcome measured were found. The authors concluded that anthracyclines are likely to be effective against childhood ALL but there is insufficient data comparing different types of anthracyclines to draw firm conclusions on differences in event rates.

Yoon et al (2009) reported results obtained by modifying the dose of idarubicin in the original Children's Cancer Group (CCG)-1884 protocol, and retrospectively comparing the results.

Twenty-eight patients diagnosed with relapsed ALL received induction chemotherapy according to the CCG-1884 protocol. The CR rate in all patients after induction chemotherapy was 57%. The idarubicin 10 mg/m^2/week group showed CR rate of 74%, compared with the 22% CR rate of the idarubicin 12.5 mg/m^2/week group (p=0.010). Remission failure due to treatment-related mortality (TRM) was 44% and 5.2% in the idarubicin 12.5 mg/m^2/week and 10 mg/m^2/week groups, respectively (p=0.011). Overall survival and 4-yr EFS EFS were 12.8% and 10.3%, respectively. Overall Survival and 4-yr EFS were higher in the idarubicin 10 mg/m^2/week group (19.3% and 15.6%) than in the 12.5 mg/m^2/week group (0% and 0%). In conclusion, a modified dose of idarubicin from 12.5 mg/m^2/week to 10 mg/m^2/week resulted in an improved CR rate in the treatment of relapsed ALL, which was due to lower TRM. However, despite improved CR rate with modified dose of idarubicin, survival rates were unsatisfactory.

Horton and Steuber (2011)

Susceptibility to Anthracycline-Induced Cardiac Toxicity in Paediatric Patients

The published literature does not directly examine the relationship between idarubicin and the incidence of cardiotoxicity in children. The cardiotoxic effects of anthracyclines, including doxorubicin and daunorubicin, in children have been demonstrated in a number of studies, are well documented in the literature, and suggest younger age at diagnosis and treatment as a risk factor.

On the basis that idarubicin is similar to daunorubicin in pharmacology and toxicology, exhibits similar cardiotoxicity to that of other anthracyclines, and is indicated for use in children, the MAH updated the idarubicin CDS in May 2007 to include the following class warning/precaution statement regarding increased susceptibility of children to anthracyclineinduced cardiotoxicity:

In infants and children there appears to be a greater susceptibility to anthracycline-induced cardiac toxicity, and a long-term periodic evaluation of cardiac function has to be performed (Lincoff 2007 - Lincoff 2007 is not a publication but, according to the list of references “2.5 Clinical Overview, Idarubicin hydrochloride. A clinical expert report to support safety revisions to the Core Data Sheet. 10 August 2007.).

Summary of Adverse Events

The MAH’s safety database contains cases of AEs reported spontaneously, cases reported by health authorities, cases published in the medical literature, and cases of serious AEs reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. The safety database was searched for all medically confirmed idarubicin cases in paediatric patients (where age was reported as ≤ 17 years) reported from international birth date for idarubicin (29 November 1989) through 31 March 2011.

Overall, the MedDRA SOCs containing the greatest number of adverse events were Infections and infestations (68 events), Blood and lymphatic system disorders (48), General disorders and administration site conditions (40), Gastrointestinal disorders (35), and Respiratory, thoracic and mediastinal disorders (19).
The AEs reported in 3 or more (≥ 2%) of the medically confirmed idarubicin paediatric cases are presented in Table 3. For comparison, the data are also presented from the entire 2,822 medically confirmed cases in the safety database.

Table 3. Summary of Adverse Events Reported in ≥ 2% Medically Confirmed Idarubicin Paediatric Cases

MedDRA SOC MedDRA Preferred Term: n (%)	Medically Confirmed Paediatric Cases (n = 118)*	All Medically Confirmed Cases (n = 2822)*
Blood and lymphatic system disorders		
Bone marrow failure	12 (9.4%)	144 (5.1%)
Febrile neutropenia	4 (3.1%)	185 (6.6%)
Leukopenia	5 (3.9%)	176 (6.2%)
Neutropenia	7 (5.5%)	153 (5.4%)
Pancytopenia	13 (10.2%)	308 (10.9%)
Cardiac disorders		
Cardiac failure	**5 (3.9%)**	**74 (2.6%)**
Cardiomyopathy	**3 (2.3%)**	**11 (0.4%)**
Gastrointestinal disorders		
Abdominal pain	3 (2.3%)	35 (1.2%)
Caecitis	3 (2.3%)	10 (0.4%)
Diarrhoea	4 (3.1%)	102 (3.6%)
Gastrointestinal haemorrhage	5 (3.9%)	39 (1.4%)
Nausea	3 (2.3%)	74 (2.6%)
Stomatitis	4 (3.1%)	82 (2.9%)
Vomiting	7 (5.5%)	88 (3.1%)
General disorders and administration site conditions		
Condition aggravated	3 (2.3%)	35 (1.2%)
Mucosal inflammation	3 (2.3%)	44 (1.6%)
Pain	3 (2.3%)	28 (1.0%)
Pyrexia	20 (15.6%)	265 (9.4%)
Hepatobiliary disorders		
Liver injury	4 (3.1%)	53 (1.9%)
Infections and infestations		
Aspergillosis	3 (2.3%)	9 (0.3%)
Infection	18 (14.1%)	266 (9.4%)
Pneumonia	5 (3.9%)	151 (5.4%)
Sepsis	19 (14.8%)	295 (10.5%)
Staphylococcal sepsis	3 (2.3%)	10 (0.4%)
Investigations		
Alanine aminotransferase increased	3 (2.3%)	12 (0.4%)
Metabolism and nutrition disorders		
Decreased appetite	5 (3.9%)	81 (2.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Myelodysplastic syndrome	3 (2.3%)	24 (0.4%)
Respiratory, thoracic and mediastinal disorders		
Respiratory failure	3 (2.3%)	41 (1.5%)
Skin and subcutaneous tissue disorders		
Rash	4 (3.1%)	39 (1.4%)

Abbreviation: n=number
*Cumulative through 31-March-2011

Of the 30 AEs listed in Table 3 that occurred in □2% cases, most were listed or consistent with listed events in the idarubicin CDS (2008). The unlisted events included caecitis, cardiomyopathy, pain, liver injury, and respiratory failure. On review of the previous PSURs, these events did not reveal any specific or new safety concerns in the paediatric population.

Assessor's comment

The requested review of publications does not add relevantly to the previous conclusion of the RMS: A positive benefit-risk ratio of (second line) idarubicin compared to daunorubicin in ALL of childhood has not been confirmed.

The CMSs should take into account that in contrast to AML anthracyclines do not have a comparable role in (first remission induction of) ALL - See e.g. “Horton and Steuber (2011) report on common treatment protocols for the treatment of ALL. Induction therapy usually involves weekly administration of vincristine for 3 to 4 weeks, daily corticosteroids (prednisone, prednisolone, or dexamethasone), and asparaginase, either as PEG-asparaginase or as 6 to 12 doses of L-asparaginase. A fourth agent such as an anthracycline (eg, doxorubicin or daunorubicin) may be added to the 3-dose regimen, particularly for high-risk patients.. Actually, the MAH has obviously no own data demonstrating a positive-benefit of idarubicin in first remission induction, or second line treatment. **Therefore, the RMS is not in the position to recommend an <u>indication</u> for idarubicin in ALL.**

In addition, also for the lower relevance of anthracyclines in the treatment of ALL, specific recommendations of idarubicin are lacking in the guidelines.

The newly submitted literature overview reveals two remarkable results:

Dinndorf et al (1997) investigated the hMTD of idarubicin in combination with fludarabine and cytarabine in 7 patients with relapsed or refractory AML, 3 with ALL (ALL), and 1 with CML. They concluded that “*this combination is active in patients with relapsed or refractory **<u>AML</u>**.*”

The observation by Yoon et al (2009) that a modified dose of idarubicin from 12.5 mg/m^2/week to 10 mg/m^2/week resulted in an improved CR rate in the treatment of relapsed ALL, which was due to lower TRM fits with the pattern of a to 8 of 10 mg/m^2/per day (x3) reduced dose in childhood AML (first remission induction).

Taken into account the safety result of table 3, in particular results as to ‘cardiac disorders’, as well as the considerations displayed for a class effect of anthracyclines, it is agree that idarubicin SmPCs/PLs shall warn for a higher cardiotoxicity/anthracycline susceptibility in children. Otherwise there is no clear pattern for a different safety profile in children and adults, information which can be included into idarubicin SmPCs/PLs.

Question # 6

6. The MAH should discuss a potential therapeutic place of oral idarubicin in ALL of childhood.

Response of the MAH

<u>Benefit and Risk Conclusions</u>

On the basis of the results reported in the studies included in this submission, idarubicin is beneficial in the paediatric population. The available study reports, literature, and safety data reviewed in this document suggest a favorable benefit/risk profile for idarubicin for the treatment of ALL in children. The reported myelosuppression and hematologic dysfunction is expected as a result of the nature of the disease process and the physiologic effects of chemotherapy in this clinical situation.

The MAH CDS states that for ALL in children, the recommended single-agent IV dosage is 10 mg/m^2 daily for 3 days. The proposed SmPC and Patient Information Leaflet for the paediatric work sharing procedure do reflect the CDS text.

The proposed EU SmPC will include the following paediatric text:

In children with ALL, the recommended single-agent intravenous dose is 10 mg/m2 daily for 3 days.

Assessor's comment

Question # 6 referred to the benefit-risk of oral idarubicin. The answer proposes an intravenous dosage.

The RMS concludes therefore that currently the benefit risk of oral idarubicin in childhood ALL is negative. As to the benefit-risk assessment for idarubicin iv in childhood ALL see assessor's comment on response of MAH to question # 5.

Question # 7

7. The MAH should address the differences in response and PK related to upregulation of Multi-Drug Resistance (MDR) enzymes and by doing so additionally sort out the mode of administration, which might be altered due to overexpression of MDR enzymes in the intestine of heavily treated patients influencing oral absorption

Response of the MAH

Review of the literature by the MAH did not reveal any studies that assessed the binding characteristics of idarubicin and its metabolite to MDR or transport proteins such as P-glycoprotein. However, in-vitro studies were noted that suggested alternation in the in-vitro cellular kinetics and / or cytotoxicity of idarubicin in the presence of inhibitors of MDR transport proteins. As an example, a study by Roovers (1999) demonstrated a 10 to 50-fold higher potency of idarubicin compared with daunorubicin and doxorubicin in the MDR variant cell lines that overexpress Pgp; the difference in cytotoxicity was lower in the sensitive parental cell line (3-fold). These results are explained by a better intracellular uptake of idarubicin compared to other anthracyclines due to its high lipophilicity in P-gp over-expressing cell lines (Roovers 1999).
Review of the literature did not reveal any studies that assessed the oral PK of idarubicin as it relates to over-expression of MDR related transporters. A couple of studies were noted that attempted to address the reversal of MDR by use of compounds that wound inhibit the drug transport. In one study (Bauer 2005), the PK of IV idarubicin when administered with and without a P-glycoprotein inhibitor, PSC-833, was examined in 15 patients with leukemia at 3 idarubicin dose levels (6, 8 and 10 mg/m^2). The mean (standard deviation, SD) clearance of idarubicin was 140 (200) and 181 (94.3) L/h for idarubicin alone and with PSC-833, respectively. The authors concluded PSC-833 did not significantly alter the disposition of idarubicin. In another study, 46 adult patients with acute non-lymphocytic leukemia were assigned to receive the same standard chemotherapy regimen of arabinosyl cytosine and idarubicin, without or with cyclosporine, an inhibitor of P-gp (Damiani 1988). Twenty-eight (28) patients received 36 courses of chemotherapy without cyclosporine A (CsA) and 18 patients received 32 courses of chemotherapy with CsA. The authors noted that the idarubicin AUC was about twice as high in the cases that received CsA than in the other cases. Furthermore, cyclosporin-treated patients had greater, and more severe, oral and intestinal mucosal toxicity, with more severe AEs,

including more cases of gram-negative bacteremia, and with a delayed hemopoietic recovery. The authors concluded that coadministration of P-gp inhibitor, CsA, would substantially increase the hemopoietic and mucosal toxicity and that the increase is accounted for, at least in part, by an increase of total body exposure to idarubicin.

In summary, there is inconclusive evidence regarding the involvement of MDR transporters on the pharmacokinetics of idarubicin. Furthermore, no information was identified by MAH that would allow an assessment for MDR overexpression and oral route of administration for idarubicin.

Assessor's comment

Question # 7 is not specifically related to idarubicin use in children but to use of oral idarubicin in heavily pre-treated, in particular MDR patients trying to sort out the better mode of administration of idarubicin.

The MAH has displayed the limited knowledge on MDR, and transport proteins.

Underlining the inconclusive evidence regarding the involvement of MDR transporters on the pharmacokinetics of idarubicin the RMS would like to add that currently the relative oral bioavailability of idarubicin in children is undetermined. This lack of knowledge concerns previously untreated as well as heavily treated (or primarily refractory) patients with childhood AML (or ALL).

VIII. 2ND REQUEST FOR SUPPLEMENTARY INFORMATION

1. As a decreased clearance (e.g. due to hepatic or renal impairment) should usually result in a prolonged terminal half-life, the pattern decreased Cl_{tb} and shortened $t_{1/2}$ for idarubicin in children displayed by the MAH could mean that children half a considerably larger Vd - T1/2 ~ (0.693)*V/Cl, see http://tpx.sagepub.com/content/23/2/115.full.pdf - than adults. A larger Vd in children, however, has not been reported (see e.g. the 562 L/m^2 in table 1 above). The observed/reported differences in PK of adults vs. children, thus, need still discussion. The MAH was requested for a discussion of these differences and make adequate proposals for a wording in sec. 5.2 of the SmPC.
2. The MAH should clarify whether the NCCN Guidelines for AML comprised in 2011 actually a *"recommend dose regime for paediatric patients for idarubicin as first-line treatment"*. The NCCN Clinical Practice Guidelines in Oncology, AML, version 2.2013 - See http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (last visit 10.03.2013) - states (p. MS-2): *"The AML Panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) convenes annually to update guidelines for the diagnosis and treatment of AML **in adults***.

IX. ASSESSMENT OF RESPONSES TO 2ND REQUEST FOR SUPPLEMENTARY INFORMATION

Question 1

As a decreased clearance (e.g. due to hepatic or renal impairment) should usually result in a prolonged terminal half-life, the pattern decreased Cl_{tb} and shortened $t_{1/2}$ for idarubicin in children displayed by the MAH could mean that children half a considerably larger Vd - T1/2 ~ (0.693)*V/Cl, see http://tpx.sagepub.com/content/23/2/115.full.pdf - than adults. A larger Vd in children, however, has not been reported (see e.g. the 562 L/m^2 in table 1 above). The observed/reported differences in PK of adults vs. children, thus, need still discussion. The MAH was requested for a discussion of these differences and make adequate proposals for a wording in sec. 5.2 of the SmPC.

Response to Q1

Pharmacokinetics (PK) of idarubicin were evaluated in 7 pediatric patients following intravenous (IV) administration of 15 to 40 mg/m^2/3-day course of idarubicin treatment, that resulted in a median idarubicin half life of 8.5 hrs (range: 3.6 – 26.4 hr).[2] In a separate study in 15 pediatric patients, following oral administrations of 30 to 50 mg/m^2/3-day course of idarubicin treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7 – 16.7 ng/mL at 40 mg/m^2 dose) and the median terminal half life was 9.2 hrs (range: 6.4 - 25.5 hrs)[3] . The observed terminal half life values of idarubicin after IV and oral administrations were comparable, indicating a similar elimination rate of idarubicin from the body in pediatric patients.
In adults, following oral administration of 10 to 60 mg/m^2 idarubicin treatment, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4 - 12.65 ng/mL achieved in 1 to 4 hours after dosing, and the plasma concentration was declined with a terminal half life of 12.7±6.0 hrs (mean±SD) [4,5]. Following intravenous administration of idarubicin in adults, the terminal half life was 13.9±5.9 hrs[4] , that was similar to that observed after the oral administrations, suggesting a similar elimination pattern of idarubicin from the body following intravenous and oral administrations in adults.
These PK data suggest that the maximum plasma concentrations of idarubicin are approximately comparable between pediatrics (i.e., median: 10.6 ng/mL, range: 2.7 – 16.7 ng/mL) and adults (i.e., mean: 12.65 ng/mL) following oral administrations.
Following both oral and IV administrations, the elimination half life values of idarubicin in pediatrics (i.e., median: 8.5 hrs, range 3.6 – 26.4 hrs for IV; median: 9.2, range: 6.4 - 25.5 hrs for oral) are comparable to that in adults (i.e., mean 12.7 hrs oral and 13.9 hrs IV), suggesting a similar elimination of idarubicin from the body in pediatrics and adults.

Total body clearance values of 30-107.9 L/h/m^2 for idarubicin have been noted for adults while the clearance reported for the pediatric population were on the lower range reported from 18-33 L/h/m^2. Although, the extent of the two ranges is different, there is some overlap between the adult and pediatric values. Idarubicin has a very large volume of distribution in both adults and pediatric patients, suggesting that much of the drug is bound to tissues.

Despite variability in pharmacokinetic parameters between patients (i.e., pediatrics and adults) and studies and relatively small number of subjects evaluated within each study, the majority of studies provided similar overall pharmacokinetics of idarubicin in pediatric and adult patients.

On the basis of the results reported in these 4 studies, the MAH proposes to include the following additional text (underlined below) in Section 5.2 of the idarubicin EU SmPC:

''Pharmacokinetic measurements in 7 pediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2/3 day course of treatment, showed a median idarubicin half life of 8.5 hr (range: 3.6 – 26.4 hr). The active metabolite, idarubicinol, accumulated during the 3 day therapy, exhibiting a median half life of 43.7 hr (range: 27.8-131 hr). In a separate study, pharmacokinetic measurements in 15 pediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2/3 day course of treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7 – 16.7 ng/mL at 40 mg/m^2 dose) showed a median terminal half life of idarubicin of 9.2 hr (range: 6.4-25.5 hr). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half life value of idarubicin after IV was comparable to that following oral administration in pediatric patients.

In adults, following oral administration of 10 to 60 mg/m^2 idarubicin treatment, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4 -12.65 ng/mL achieved in 1 to 4 hours after dosing, and the plasma concentration was declined with a terminal half life of 12.7±6.0 hrs (mean±SD). Following intravenous administration of idarubicin in adults, the terminal half life was 13.9±5.9 hrs , similar to that observed after the oral administration.

Consequently, the maximum plasma concentrations of idarubicin are approximately comparable between pediatrics and adults following oral administrations.

Following both oral and IV administrations, the elimination half life values of idarubicin in pediatrics and adults are similar.
Total body clearance values of 30-107.9 L/h/m^2 for idarubicin have been noted for adults while the clearance reported for the pediatric population were on the lower range reported from 18-33 L/h/m^2. Although, the extent of the two ranges is different, there is some overlap between the adult and pediatric values. Idarubicin has a very large volume of distribution in both adults and pediatric patients, suggesting that much of the drug is bound to tissues.

References:

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Br J Clin Pharmacol 1987;23:303-310.
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Clin Pharmacol Ther 1986;40:643-9.

Assessment of response to question 1

In general, the comments of the MAH, that the variability of the presented PK data is high, that the studies presented are small, and that comparing adult and paediatric data means not a randomized comparison so that differences may be (partially) explained by methodological reasons, can be followed.

The assessor is of the opinion that elimination kinetics is comparable after oral and intravenous administration of idarubicin. This is and expected result. These statements apply on each age group separately. This observation, however, argues against major methodological differences in the different trials summarized in table 1 'Mean pharmacokinetic parameters in Patients with Various Types of Cancer Receiving Intravenous or Oral Dose of Idarubicin' above.

However, in contrast to the MAH the assessor is of the opinion that elimination kinetics (not the by the MAH also discussed c_{max}) in adults and children differ (compare terminal half-life of idarubicin iv of 8.5 vs. 13.9 hrs in children and in adults respectively, the hardly overlapping range of Cl_{tb} of 18-33 vs. 30-107.9 L/h/m^2 in children and in adults respectively, as well as the overall smaller Vd in children compared to adults (please refer to table 1 above)).

The trends, shorter terminal half-life, lower total body clearance, and smaller apparent volume of distribution in children compared to adults do not fully fit together, or are not fully explainable by their typical inter-relationship ($T_{1/2}$ ~ (0.693)*V/Cl).

For the question how to label those observations within the scope of an article 45 procedure, the assessor is in favor of adding the data reported/published in children, as well as comparing these with adult data. But a difference should be called a difference but not "similar", even if the differences are difficult to explain by pattern.

Consequently, the assessor proposes the following changes in addition to the (most recent) proposals of the MAH (underlined new proposals of the MAH, overwriting modus used by assessor):

> "Pharmacokinetic measurements in 7 paediatric patients receiving intravenous idarubicin in doses ranging from 15 to 40 mg/m^2 during the 3 days of treatment, showed a median idarubicin half-life of 8.5 hrs (range: 3.6 – 26.4 hrs). The active metabolite, idarubicinol, accumulated during the 3 days of treatment, exhibiting a median half-life of 43.7 hrs (range: 27.8-131 hrs). In a separate study, pharmacokinetic measurements in 15 paediatric patients receiving oral idarubicin in doses ranging from 30 to 50 mg/m^2 during the 3 days of treatment, the maximum plasma concentration of idarubicin was 10.6 ng/mL (range 2.7 – 16.7 ng/mL at the 40 mg/m^2 dose). The median terminal half-life of idarubicin was 9.2 hrs (range: 6.4-25.5 hrs). Significant accumulation of idarubicinol was seen over the 3 day treatment period. The observed terminal half-life value of idarubicin after IV was comparable to that following oral administration in paediatric patients.
>
> In adults, following oral administration of 10 to 60 mg/m^2 idarubicin, idarubicin was rapidly absorbed with the maximum plasma concentrations of 4 -12.65 ng/mL achieved in 1 to 4 hours after dosing. The terminal half-life was 12.7±6.0 hrs (mean±SD). Following intravenous administration of idarubicin in adults, the terminal half-life was 13.9±5.9 hrs , similar to that observed after the oral administration.
>
> Since c_{max} of idarubicin is similar in children and adults following oral administrations, absorption kinetics seem not to differ between adults and children.

Following both oral and IV administrations, the elimination kinetics of idarubicin in children and adults differ:

Elimination half-life is shorter in children compared to adults.
Total body clearance values of 30-107.9 L/h/m^2 for idarubicin reported for adults are higher than clearance values in the range of 18-33 L/h/m^2 reported for paediatric populations . Althoughidarubicin has a very large volume of distribution in both adults and children ~~pediatric patients~~ suggesting that much of the drug is bound to tissues, the shorter elimination half-life and lower total body clearance are not entirely explained by a smaller apparent volume of distribution in children compared to adults."

Question 2

The MAH should clarify whether the NCCN Guidelines for AML comprised in 2011 actually a *"recommend dose regime for paediatric patients for idarubicin as first-line treatment"*. The NCCN Clinical Practice Guidelines in Oncology, AML, version 2.2013 - See http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (last visit 10.03.2013) - states (p. MS-2): *"The AML Panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) convenes annually to update guidelines for the diagnosis and treatment of AML **in adults***.

Response to Q2

Although the NCCN guidelines are focused in adults, the general principles of therapy for adolescents with acute myeloid leukemia (AML) are applied to children. Optimal treatment of acute myeloid leukemia (AML) requires control of bone marrow and systemic disease. Chemotherapy is the first line of defence beginning with induction therapy and idarubicin plays a critical role.

Induction Chemotherapy of newly diagnosed and refractory or relapsed paediatric patients

Current paediatric AML protocols result in 85% to 90% complete remission rates. Of those patients who do not achieve remission, about one-half have resistant leukemia and one-half die from the complications of the disease or its treatment. The two most effective drugs used to induce remission in children with AML are cytarabine and an anthracycline. **The anthracyclines that have been most used in induction regimens for children with AML are daunorubicin and idarubicin**

Even with induction rates approaching 90%, relapse remains the primary reason for death in this population, indicating a need for improvement in post-remission therapy. Children with refractory and relapsed leukemia, as well as children with a secondary AML, have a poor prognosis, and alternative induction therapies to achieve repeat remission are required but they are very limited. High-dose Ara-C is one of the most effective drugs in reinduction therapy of poor-prognosis acute leukemia which acts synergistically with fludarabine, anthracyclines, and G-CSF. The addition of idarubicin to the combination of high-dose Ara-C and fludarabine with or without G-CSF increased the CR rate to 67% to 80% in pediatric cases with refractory or relapsed AML compared to CR rates of 50% to 60% that the fludarabine and high-dose Ara-C with or without G-CSF alone produced.

In a recent Phase 2 clinical trial involving 104/109 valuable paediatric patients with AML at first relapse, the novel combination of 2-chlorodeoxyadenosine (2-CDA) (8 mg/m^2 per d x 5 d) plus idarubicin (Ida) (10 mg/m^2 per d x 3 d) produced an overall response rate of 51% (complete

response [CR] + partial response) with a CR rate of 46%. Two-year event-free survival (EFS) and overall survival (OS) were 20% and 26%, respectively. There was an acceptable toxicity profile with one neurological event and no cardiac events observed. This study demonstrated that the novel combination of 2-CDA/Ida was effective and should be considered for incorporation in front line therapy for children with AML.

In addition to the previously provided literature references to support the use of idarubicin in the continuum of treatment in children with AML, the International BFM Study Group [7] and the AML International Expert panel Committee[8] standards for the management, diagnosis, response assessment, and treatment in childhood
AML are submitted for your review. A high level summary from these references is given below.

AML Committee of the International BFM Study Group

Recommendation

Children with AML should be treated within controlled clinical trials. Treatment of childhood AML requires an intensive anthracycline- and cytarabine-based therapy using at least 4 or 5 courses.

Induction

One or 2 courses of induction therapy are routinely used in children and adults. Standard induction therapy comprises 3 days of an anthracycline (eg, daunorubicin at least 60 mg/m^2, idarubicin 10-12 mg/m^2, or the anthracenedione mitoxantrone 10-12 mg/m^2) and 7-10 days of cytarabine (100-200 mg/m^2 continuously or twice daily intravenously; ie, “3+7” or “3+10”).With these regimens, >85% of children and adolescents achieve complete remission (CR). Although a third drug, such as etoposide or 6-thioguanine, is commonly included in induction, their benefit has not been proven.

Practice Guidelines by the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

The Italian Society of Hematology and two affiliated societies (SIES and GITMO) commissioned a project to an Expert Panel aimed at developing clinical practice guidelines for acute myeloid leukemia treatment. After a systematic comprehensive literature review, the Expert Panel formulated recommendations for the management of primary acute myeloid leukemia (with the exception of acute promyelocytic leukemia) and graded them according to the supporting evidence. When evidence was lacking, consensus-based statements have been added.

Recommendation

First-line therapy for all newly diagnosed patients eligible for intensive treatment should receive, as soon as possible, one cycle of “standard induction therapy” including cytarabine (100-200 mg/m2/day), administered by continuous seven day long intravenous infusion and one of the following agents, administered for three days: daunorubicin (45-60 mg/m^2/day), idarubicin (10 mg/m^2/day), mitoxantrone (10 mg/m^2/day). After the first induction course, all children who achieve a complete or partial response and the adults who achieve a partial response should receive a second induction course.

A comparison between anthracyclines given in association with cytarabine was investigated by different groups. Idarubicin appeared to be more effective than daunorubicin, though the doses of idarubicin and daunorubicin may not have been equivalent. A meta-analysis of randomized trials comparing idarubicin (usually at the dosage of 10-12 mg/m^2/day for three days) and daunorubicin (45-60 mg/m^2) showed that the use of idarubicin in association with cytarabine resulted in a higher CR rate 80% compared to the 65% CR of the daunorubicin plus cytarabine conventional two drug regimen.[9]

Despite major improvements in outcome over the past decades, acute myeloid leukemia (AML) remains a life-threatening malignancy in children, with current survival rates of~ 70%. Fewer than 10% of people with AML are children.

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6. Chaleff S, Hurwitz CA, Chang M, et al.: Phase II study of 2-chlorodeoxyadenosine plus idarubicin for children with acute myeloid leukaemia in first relapse: a paediatric oncology group study. Br J Haematol 156 (5): 649-55, 2012.
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Assessment of response to question 2

In response to the question, actually directed to the question of recommended idarubicin in children with AML, the MAH provides now a comprehensive review of literature, therapeutic guidelines as well as meta-analysis.

In general, this review further supports the very initial view of the RMS (based originally in particular on the series of BFM trials), i.e. that idarubicin (iv) should be indicated/may have the same indication as in adults, i.e. (at least in the RMS based on a national MAA) in combination with cytarabin as "first line" (i.e. previously not treated) remission induction (and consolidation/second induction) treatment of AML.

The RMS recommends granting such an indication.

As to the specific question which is the "*dose regime for paediatric patients for idarubicin as first-line treatment"* recommended by NCCN, the MAH seems to agree that NCCN had not recommended doses of idarubicin in children with AML.

However, there are other (trials and) recommendation (BFM group and SIES/GITMO), allowing to conclude that an (iv) dose of 10-12 mg/m^2 x 3 days, in combination with cytarabin, can be recommended in the first (and second) remission induction treatment of children with AML.

Point resolved

X. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	AS	ATC-Code (7-digit)
PFIZER	AT	Zavedos 10mg - Kapseln "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 10mg - Trockenstechampulle "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 10mg - Durchstichflasche "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 20mg - Trockenstechampulle "PFIZER"	20 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 20mg - Durchstichflasche "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 25mg - Kapseln "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 5mg - Kapseln "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	AT	Zavedos 5mg - Trockenstechampulle "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	AT	Zavedos 5mg - Durchstichflasche "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 10mg - Kapseln "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 10mg - Trockenstechampulle "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 10mg - Durchstichflasche "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 20mg - Trockenstechampulle "PFIZER"	20 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 20mg - Durchstichflasche "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 25mg - Kapseln "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 5mg - Kapseln "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	BE	Zavedos 5mg - Trockenstechampulle "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	BE	Zavedos 5mg - Durchstichflasche "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BG	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	BG	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	BG	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	BG	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	CY	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	CZ	Zavedos 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	CZ	Zavedos Inj. "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	CZ	Zavedos 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	CZ	Zavedos 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06

PFIZER	CZ	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DK	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DK	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	EE	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	EE	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	EE	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	EE	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FI	Zavedos "PFIZER"	1 mg/ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FI	Zavedos 1mg/ml Injektioneste "PFIZER"	1 mg/ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FI	Zavedos 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06

PFIZER	FI	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FI	Zavedos 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	FI	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	20 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06

PFIZER	FR	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	FR	Zavedos "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Idamycin Oral 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos Oral 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos (10mg) "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Idarubicin P and U 10mg/10ml "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos 10mg/10ml "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos (20mg) "PFIZER"	20 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Idarubicin P and U 20mg/ml "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos 20mg/20ml "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	DE	Idamycin Oral 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos Oral 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	DE	Idamycin Oral 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos Oral 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos 5mg "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Idarubicin P and U 5mg/5ml "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	DE	Zavedos 5mg/5ml "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	EL	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	EL	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	EL	Zavedos Injectable Solution 10mg/10ml "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	EL	Zavedos "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	EL	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	EL	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	EL	Zavedos "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	HU	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	HU	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	HU	Zavedos "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	HU	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	HU	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IS	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	IS	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IE	Zavedos Capsules 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	IE	Zavedos 10mg Powder for Solution for Injection "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IE	Zavedos Capsules 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	IE	Zavedos Injection 5mg "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IT	Zavedos 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	IT	Zavedos 10mg "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IT	Zavedos 10mg/10ml "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IT	Zavedos 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06

PFIZER	IT	Zavedos 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	IT	Zavedos 5mg/5ml "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	IT	Zavedos 5mg/5ml "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LV	Zavedos 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	LV	Zavedos 10mg "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LV	Zavedos 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	LV	Zavedos 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	LV	Zavedos 5mg "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LT	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LT	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	LU	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos Cyto Vial "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos Cyto Vial "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	LU	Zavedos Cyto Vial "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	NL	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	NL	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	NO	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	NO	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PL	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PL	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos Oral "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos CS "PFIZER"	10 mg/10ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos "PFIZER"	20 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos CS "PFIZER"	20 mg/20ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos Oral "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06

PFIZER	PT	Zavedos Oral "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	PT	Zavedos CS "PFIZER"	5 mg/5ml	Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	RO	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	RO	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	SK	Zavedos 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	SK	Zavedos 10mg "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	SK	Zavedos 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	SK	Zavedos 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	SK	Zavedos 5mg "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	SL	Zavedos 10mg Powder for Solution for Injection "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	ES	Zavedos Oral 10mg "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	ES	Zavedos 10mg Inyectable "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	ES	Zavedos Oral 25mg "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	ES	Zavedos Oral 5mg "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	ES	Zavedos 5mg Inyectable "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	SE	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	SE	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	SE	Zavedos "PFIZER"	20 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06

PFIZER	SE	Zavedos "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	SE	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	SE	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	UK	Zavedos "PFIZER"	10 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	UK	Zavedos "PFIZER"	10 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06
PFIZER	UK	Zavedos "PFIZER"	25 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	UK	Zavedos "PFIZER"	5 mg	Capsule, Hard, Oral	idarubicin HCl	L01DB06
PFIZER	UK	Zavedos "PFIZER"	5 mg	Powder Freeze Dried For Solution, For Injection, IV	idarubicin HCl	L01DB06