TRANSPARENCY COMMITTEE
Opinion
2 April 2014

CERUBIDINE 20 mg, powder for solution for infusion
B/10 vials (CIP: 34009 550 480 5 3)

Applicant: SANOFI-AVENTIS FRANCE

<table>
<thead>
<tr>
<th>INN</th>
<th>daunorubicin</th>
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<tbody>
<tr>
<td>ATC code (2013)</td>
<td>L01DB02 (anthracyclines and related substances – daunorubicin)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Extension of indication</td>
</tr>
<tr>
<td>List(s) concerned</td>
<td>Inclusion for hospital use (French Public Health Code L. 5123-2)</td>
</tr>
<tr>
<td>Indication(s) concerned</td>
<td>“In children, as part of a combination chemotherapy regimen: – Acute lymphoid leukaemia – Acute myeloid leukaemia”</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>The actual benefit of CERUBIDINE 20 mg is substantial, as part of a combination chemotherapy regimen, in the treatment of acute lymphoblastic leukaemia and acute myeloblastic leukaemia in children.</td>
</tr>
<tr>
<td>Improvement in Actual Benefit</td>
<td>CERUBIDINE 20 mg does not provide any improvement in actual benefit (level V, non-existent) in the treatment of acute lymphoblastic and myeloblastic leukaemia in children.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>In the paediatric population, daunorubicin (CERUBIDINE) is primarily used in induction and intensification/consolidation therapy for acute lymphoblastic leukaemia and acute myeloblastic leukaemia.</td>
</tr>
<tr>
<td>Target population</td>
<td>The target population for this indication can be estimated at 500 patients.</td>
</tr>
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</table>
01   ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>04/12/1997 (national procedure); Date of last revision: 23/11/2011 (extension of indication)</th>
</tr>
</thead>
</table>
| Prescribing and dispensing conditions / special status | List I  
Medicine for hospital prescription only.  
Prescription restricted to oncology or haematology specialists or doctors with cancer training.  
Medicinal product requiring special monitoring during treatment. |
| ATC Classification | 2013  
L  Antineoplastic and immunomodulating agents  
L01  Antineoplastic agents  
L01D  Cytotoxic antibiotics and related substances  
L01DB  Anthracyclines and related substances  
L01DB02  Daunorubicin |

02   BACKGROUND

Application for inclusion of CERUBIDINE 20 mg on the list of medicines approved for hospital use in the extended indication: treatment of childhood acute lymphoblastic leukaemia and childhood acute myeloblastic leukaemia. This extended indication results from a European SPC standardisation initiative relating to daunorubicin’s use in paediatrics.

The use of daunorubicin to treat acute leukaemia as part of a combination chemotherapy regimen has been described in the literature since the late 1970s and is common in clinical practice today.

CERUBIDINE has been included on the list of medicines approved for hospital use since 31/07/1986. On 2 February 2005, the Transparency Committee concluded that the actual benefit of this proprietary medicinal product was substantial in its adult Marketing Authorisation indications.

03   THERAPEUTIC INDICATIONS

“– Acute leukaemias  
– Acute transformation of chronic myeloid leukaemia  
– Hodgkin and non-Hodgkin lymphoma

In children, as part of a combination regimen:  
– Acute lymphoid leukaemia (ALL)  
– Acute myeloid leukaemia (AML)”
04 DOSEAGE

“Paediatric population:
The dosage is usually calculated based on body surface area and adjusted as needed, depending on clinical response and patients’ haematological status. Specific protocols and current guidelines should be consulted for recommended treatments and combinations.
Courses may be administered 1 to 6 weeks apart.
In children aged over 2 years, the risk of cardiotoxicity starts from a cumulative dose of 300 mg/m^2.
In children aged under 2 years (or with a body surface area under 0.5 m^2), the maximum cumulative dose is 10 mg/kg.”

“No controlled studies have been conducted in the paediatric population.”

05 THERAPEUTIC NEED

The acute leukaemias are a heterogeneous group of haematological malignancies characterised by a clonal proliferation of myeloid or lymphocyte precursors and by impaired haematopoiesis. As these conditions are life-threatening, diagnosis and treatment are a matter of urgency.
Acute leukaemias are the most common cancers in children aged under 15 years.\(^1\) Acute lymphoblastic leukaemia accounts for over three-quarters of childhood acute leukaemias, with a peak incidence between the age of 1 and 4 years. Acute myeloblastic leukaemia is a serious disease but rarer in children.
Therapeutic management must be started rapidly with a combination chemotherapy regimen (induction, consolidation, intensification, maintenance) and supportive care to enhance the chemotherapy. In some cases, a haematopoietic stem cell transplant (HSCT) may be considered.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Indications</th>
<th>Opinion date</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursed Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRIBLASTIN 10 mg/5 ml, 20 mg/10 ml, 50 mg/25 ml, ADRIBLASTIN 200 mg/100 ml, solution for injection for infusion in vial – 10 mg, lyophilisate for parenteral use (infusion) in vial (doxorubicin) PFIZER HOLDING FRANCE and generics</td>
<td>– Acute and chronic leukaemias […]</td>
<td>14/02/2001</td>
<td>Substantial</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>ZAVEDOS 5 mg/5 ml, 10 mg/10 ml and 20 mg/20 ml, solution for infusion (idarubicin) PFIZER HOLDING FRANCE and generics</td>
<td>– Acute myeloblastic leukaemia – Relapsed acute lymphoblastic leukaemia</td>
<td>06/07/2011</td>
<td>Substantial</td>
<td>V</td>
<td>Yes</td>
</tr>
<tr>
<td>NOVANTRONE 10 mg/5 ml and 20 mg/10 ml, concentrate for solution for infusion (mitoxantrone) MEDA PHARMA and generics</td>
<td>[…] – Acute myeloid leukaemia: used alone, mitoxantrone obtains a complete response in 30% to 50% of relapsed patients. Combining mitoxantrone with other anticancer drugs such as cytosine arabinoside can increase the response rate. […]</td>
<td>02/02/2005</td>
<td>Substantial</td>
<td>Not allocated</td>
<td>Yes</td>
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</tbody>
</table>

06.2 Other health technologies
None.

Conclusion
The comparators listed are all clinically relevant.

07 SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Opinion date (reason for the request)</th>
<th>2 February 2005</th>
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</thead>
<tbody>
<tr>
<td>Indication</td>
<td>“– Acute leukaemias – Acute transformation of chronic myeloid leukaemia – Hodgkin and non-Hodgkin lymphoma”</td>
</tr>
<tr>
<td>Actual Benefit (wording)</td>
<td>Substantial actual benefit in all indications</td>
</tr>
<tr>
<td>IAB (wording)</td>
<td>Not allocated</td>
</tr>
</tbody>
</table>
08 ANALYSIS OF AVAILABLE DATA

In support of its application for this extended indication, the company submitted the following data:

- The European assessment report for CERUBIDINE (daunorubicin) in the treatment of acute leukaemia in paediatrics (HMA 2013\(^2\)), based on a review of the literature (1989–2008);
- A literature review complementing the European assessment (2008–2012);
- An expert report written in 1989 to obtain Marketing Authorisation for CERUBIDINE in the UK. This report will not be described here.

The published studies on the treatment of childhood acute leukaemia are mostly non-controlled studies evaluating the efficacy of combination chemotherapy regimens that generally include daunorubicin and other cytotoxic drugs, without any individual evaluation of daunorubicin.

No controlled studies specifically evaluating daunorubicin have been conducted in the paediatric population.

08.1 Efficacy

The studies submitted evaluated the efficacy of combination chemotherapy regimens in childhood acute leukaemias. Daunorubicin was one of the medicines used in these protocols. As the aim was not to evaluate the efficacy of daunorubicin in the treatment of childhood ALL and AML, the results cannot support a robust and specific evaluation of its benefit.

8.1.1 Acute lymphoblastic leukaemia

The publications on the treatment of childhood acute lymphoblastic leukaemia submitted by the company are:

- A review\(^3\) of five consecutive trials from the Berlin-Frankfurt-Münster (BFM) group of studies evaluating chemotherapy protocols. This will not be discussed here due to the type of publication.
- Three randomised, open-label studies\(^4,5,6\) from the PETHEMA (Spain), UK-MRC-ALL (UK) and BFM (Germany) groups of studies comparing the efficacy of combination chemotherapy regimens in children with newly diagnosed ALL.
- Two non-comparative studies\(^7,8\) from the DCOG (Netherlands) and BFM groups of studies evaluating combination chemotherapy regimens in children with newly diagnosed ALL.
- A randomised study\(^9\) from the Children’s Cancer Group (USA) group of studies comparing idarubicin to daunorubicin as part of a combination chemotherapy regimen in children with a first relapse of ALL.

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A study\textsuperscript{10} evaluating two methods of administering daunorubicin (rapid IV or 24-hour infusion), which will not be discussed here.

The combination chemotherapy regimens evaluated in ALL used daunorubicin (see Table 1):
- at doses of 30 to 50 mg/m\(^2\) per administration;
- administered in several different ways (rapid IV or 24-hour to 48-hour infusion);
- in different phases of combination chemotherapy (induction, intensification, consolidation, etc.);
- in various combinations of cytotoxic drugs.

In most studies, patients were stratified by whether their risk profile was low, intermediate or high.

The protocols and results from the accepted studies are presented in Table 1.
Overall, in the population of children with newly diagnosed ALL, the post-induction remission rate was high, in some cases reaching over 95%, and event-free survival at 10 years was about 70% depending on the protocol.

In the most recent study (Veerman et al. 2009), the Dutch DCOG ALL-9 protocol, where daunorubicin was only administered to high-risk patients in the induction phase, led to complete remission in 98% of included patients.

The results of all the studies, including reviews, are provided for information in Appendix 2, Table 3 of this opinion (summary tables).

Table 1. Clinical trials in children with acute lymphoblastic leukaemia (ALL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Numbers</th>
<th>Population Studied/ Inclusion Criteria</th>
<th>Treatment Regimens</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCOG ALL-9 protocol Veerman et al. 2009</td>
<td>Prospective, non-comparative study stratified by patient risk (high risk: HR and non-high risk: NHR) evaluating the DCOG ALL-9 protocol, which was enhanced in HR patients (daunorubicin added and higher methotrexate dose).</td>
<td>$n_{\text{total}} = 859$&lt;br&gt;Groups: &lt;br&gt;– non-high risk $n=601$ (NHR); &lt;br&gt;– high risk $n=258$ (HR).</td>
<td>Children aged 1 to 18 years with ALL diagnosed in the Netherlands between 1997 and 2004 (exclusions: prior treatment, age &lt; 1 year, secondary ALL and mature B-cell ALL)</td>
<td><strong>Non-high-risk group (NHR)</strong>&lt;br&gt;Induction: oral dexamethasone, IV vincristine, IV L-asparaginase, triple intrathecal therapy (methotrexate, cytarabine, prednisolone)&lt;br&gt;Consolidation: oral methotrexate, oral folic acid, triple intrathecal therapy&lt;br&gt;Maintenance: oral mercaptopurine, oral methotrexate, oral dexamethasone, IV vincristine, triple intrathecal therapy</td>
<td>– Complete remission in 98% of all patients (98.5% of non-high-risk patients and 96.9% of high-risk patients)&lt;br&gt;– Event-free survival at 5 years: 84% of non-high-risk patients and 72% of high-risk patients&lt;br&gt;– Overall survival at 5 years: 90% of non-high-risk patients and 78% of high-risk patients</td>
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<td><strong>High-risk group (HR)</strong>&lt;br&gt;Induction (quadruple therapy): same as NHR plus IV daunorubicin (25 mg/m² x 4)&lt;br&gt;Consolidation: oral mercaptopurine, high-dose oral methotrexate, oral folic acid&lt;br&gt;Intensification (2 phases):&lt;br&gt;1. IV asparaginase, IV daunorubicin (25 mg/m² x 3), oral mercaptopurine, IV vincristine, oral dexamethasone, triple intrathecal therapy&lt;br&gt;2. low-dose cytarabine, cyclophosphamide&lt;br&gt;Maintenance: same as NHR but with IV methotrexate</td>
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<thead>
<tr>
<th>Study</th>
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</table>
| PETHEMA ALL-89 protocol     | Randomised, prospective, open-label study evaluating the benefit of an early or delayed consolidation phase, stratified by ALL risk group (low: LR, intermediate: IR, high: HR) | $n_{\text{total}} = 195$ | Groups:  
- Low risk (LR): $n=89$;  
- Intermediate risk (IR): $n=50$;  
- High risk (HR): $n=56$  
Children aged under 15 years with ALL diagnosed in Spain between 1989 and 1994 (ALL-L3 excluded)  
Induction common to all patients (5 weeks)  
- $I-1$: IV vincristine, IV/oral prednisolone, IV L-asparaginase, IV daunorubicin ($30 \text{ mg/m}^2 \times 4$) and IV cyclophosphamide  
- $I-2$ in case of complete remission: high-dose methotrexate and mercaptopurine  
Consolidation  
- early C-1 (7 weeks): same as $I-1 + IV$ teniposide and IV cytosine arabinoside, with prednisolone replaced by dexamethasone  
- delayed C-2 (6 weeks): same as $I-1 + IV$ teniposide and IV cytosine arabinoside, with vincristine replaced by vindesine and daunorubicin replaced by mitoxantrone  
Maintenance  
Common to all patients (2 years) Oral mercaptopurine, IM methotrexate  
Randomisation stratified by risk  
- LR: $[I-1 + I-2]$ or $[I-1 + I-2 + C-1]$  
- IR: $[I-1 + I-2 + C-1]$ or $[I-1 + I-2 + C-1 + C-2]$  
- HR: $[I-1 + I-2 + C-1 + C-2]$  
Overall results:  
- no deaths at the end of the induction phase  
- post-induction complete remission in 97% of included patients (189/195)  
- overall survival at 10 years: 69%, 95% CI [54; 66] (LR=86%, IR=76% and HR=44%)  
- event-free survival at 10 years: 58%, 95% CI [52; 64] (LR=71%, IR=69% and HR=30%)  
Results after randomisation:  
LR group: higher event-free survival at 10 years: 62% without C-1 versus 79% with C-1 ($p=0.006$) and higher overall survival at 10 years: 66% versus 90% ($p=0.006$)  
IR group: higher event-free survival at 10 years: 52% without C-2 versus 87% with C-2 ($p=0.006$) and higher overall survival at 10 years: 61% versus 92% ($p=0.006$) |
<table>
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</thead>
<tbody>
<tr>
<td>Modified ALL-BFM 90 protocol</td>
<td>Prospective, non-comparative study evaluating the efficacy of the modified ALL-BFM 90 protocol, in terms of event-free survival, in high-risk (HR) patients</td>
<td>n&lt;sub&gt;total&lt;/sub&gt; = 374</td>
<td>Children aged under 19 years with ALL diagnosed at the study site in Argentina between 1990 and 1995 (ALL-L3 and mature B-cell ALL excluded)</td>
<td><strong>Protocol I:</strong> oral prednisone, IV vincristine, IV daunorubicin (30 mg/m² x 4), IM L-asparaginase, IV cyclophosphamide, IV cytarabine, oral 6-mercaptopurine, intrathecal methotrexate <strong>Protocol II:</strong> oral 6-mercaptopurine, IV methotrexate <strong>Protocol III:</strong> oral dexamethasone, IV vincristine, IV doxorubicin, IM L-asparaginase, IV cyclophosphamide, IV cytarabine, oral 6-tioguanine <strong>HR 1:</strong> oral dexamethasone, IV vincristine, IV methotrexate, oral 6-mercaptopurine, IV cytarabine, IM L-asparaginase <strong>HR 2:</strong> oral dexamethasone, IV vindesine, IV methotrexate, oral 6-tioguanine, IV ifosfamide, IV daunorubicin (50 mg/m² x 1), IM L-asparaginase <strong>HR 3:</strong> oral dexamethasone, IV cytarabine, IV etoposide, IM L-asparaginase <strong>Radiotherapy:</strong> cranial irradiation <strong>Maintenance</strong> common to all patients (2 years): oral mercaptopurine, IM methotrexate <strong>Protocol according to risk group</strong> – <strong>SR:</strong> protocols I+M+III + maintenance – <strong>IR:</strong> protocols I+M+II + maintenance – <strong>HR:</strong> protocols I + [HR1+2+3] x 3 + radiotherapy + maintenance</td>
<td>– Complete remission in 94.4% of patients (SR=98%, IR=97%, HR=78%) – Event-free survival at 5 years was estimated as 64%±5% for all patients (SR=74%, IR=66%, HR=37%) – Overall survival: not recorded</td>
</tr>
<tr>
<td>Study</td>
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</table>
| **CCG-1884 protocol**         | Randomised, comparative, open-label study evaluating the efficacy and toxicity of idarubicin versus daunorubicin in children with a 1st relapse of ALL | n_total = 92 | Children aged between 1 and 21 years who relapsed during their first treatment or in the following year. Enrolment in the United States from 1990 to 1992. | *Re-induction:* IV vincristine, oral prednisone, IM L-asparaginase + either idarubicin or daunorubicin  
*Maintenance (intermediate phase):* IV vincristine, IV methotrexate, IM L-asparaginase followed either by bone marrow transplant or, if there was no compatible donor, by maintenance chemotherapy  
*Maintenance:* IV cytarabine, IM L-asparaginase, IV vincristine, IV methotrexate and the same anthracycline (DNR/IDR) | – Complete remission in 73% of patients treated with IDR (32/44) and 69% of patients treated with DNR (33/48), with six deaths during induction with IDR versus none with DNR  
– No difference in event-free survival at 24 months (DNR 19% and IDR 10%; p=0.13) or overall survival at 36 months (DNR 19% and IDR 23%; p=0.88). |
| Feig et al. 1996              |                                                                                                   |          |                                                                                                     |                                                                                      |                                                                                               |
| **MSK-NY-II protocol**       | Prospective, randomised exploratory study evaluating the efficacy of four methods of administering induction therapy in the MSK-NY-II protocol | n_total = 44 | Children aged 2 to 10 years with intermediate-risk and high-risk ALL diagnosed at the study site in the United States between 1986 and 1991 (low-risk ALL excluded) | *Induction:*  
– I-A: D0: IV cyclophosphamide, D1: vincristine/prednisone, D2+D3: daunorubicin rapid IV (60 mg/m²/day)  
– I-B: D0: cyclophosphamide, D1: IV vincristine/oral prednisone, D2+D3: daunorubicin slow infusion over 48 h (120 mg/m²)  
– II-A: D0+D1: daunorubicin rapid IV (60 mg/m²/day), D2: vincristine/prednisone, D3: cyclophosphamide  
– II-B: D0+D1: daunorubicin slow infusion over 48 h (120 mg/m²) D2: vincristine/prednisone/cyclophosphamide  
*Consolidation:* IV cytosine arabinoside, IM L-asparaginase, oral methotrexate, IV vincristine, oral prednisone  
*Maintenance*  
– initial phase: notably daunorubicin rapid IV or slow infusion over 48 h (40 mg/m²)  
– subsequent phases: notably daunorubicin rapid IV or slow infusion over 48 h (40 mg/m²) | Overall results:  
– Remission in 94% of patients (41/44); three patients died before induction therapy had finished (respiratory distress <D0, brain herniation D2, gastrointestinal perforation and Pseudomonas sepsis D17)  
– Event-free survival at 4 years was estimated at 86%±10% for all included patients  
Results after randomisation:  
There was a statistically significant greater and more rapid reduction in the number of leukaemia cells in the bone marrow  
– in the group initially treated with daunorubicin versus those starting with cyclophosphamide on D2, D7 and D14 (p<0.03);  
– in the group treated with a 48-hour infusion of daunorubicin versus those treated with a rapid IV on D2 only (p<0.03); no difference on D7 or D14. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Numbers</th>
<th>Population Studied/ Inclusion Criteria</th>
<th>Treatment Regimens</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKALL VIII protocol</td>
<td>Randomised, prospective, open-label study evaluating the benefit of adding daunorubicin to a combined induction chemotherapy regimen</td>
<td>$n_{total} = 630$</td>
<td>Children aged under 14 years with ALL diagnosed in the UK between 1980 and 1984</td>
<td>Induction (4 weeks)</td>
<td>No significant difference in event-free survival at 5 years (relapse + death)</td>
</tr>
<tr>
<td>Eden et al. 1991</td>
<td></td>
<td>Groups: - without DNR $n_A=322$ - with DNR $n_B=308$</td>
<td></td>
<td>- Arm A: IV vincristine, oral prednisone, IM L-asparaginase, oral mercaptopurine</td>
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<td>- Arm B: the same + IV daunorubicin (45 mg/m² x 2)</td>
<td>- Event-free survival at 5 years approximately 55% for all patients</td>
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<td>Maintenance (2 years versus 3 years)</td>
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</tbody>
</table>
8.1.2 Acute myeloblastic leukaemia

The publications on the treatment of childhood acute myeloblastic leukaemia submitted by the company are:

- Four reviews\(^{11,12,13,14}\) of a number of studies from the AIEOP (Italy), CCG (United States) and BFM (Germany) groups of trials evaluating successive chemotherapy protocols. These studies will not be discussed here because of the type of publications.
- A randomised, open-label study\(^{15}\) comparing the efficacy of consolidation with haematopoietic stem cell transplantation with intensive chemotherapy.
- Two non-comparative studies\(^{16,17}\) evaluating combination chemotherapy regimens in children with AML.
- A post-hoc study\(^{18}\) evaluating the efficacy of the APL-93 protocol (all-trans retinoic acid plus combination chemotherapy) in a subgroup of children with acute promyelocytic leukaemia (APL). This study will not be discussed here because of its methodology.

The combination chemotherapy regimens evaluated in AML used daunorubicin (see Table 2):

- at doses of 45 to 50 mg/m\(^2\) per administration;
- always combined with cytarabine in the induction phase and, depending on the protocol, combined with 6-thioguanine or etoposide. Some protocols used daunorubicin in the post-induction (intensification/consolidation) phase.

The protocols and results from the accepted studies are presented in Table 2.

Overall, in the population of children with newly diagnosed AML, the post-induction remission rate was about 60% to 80% and event-free survival at 10 years was low, ranging from about 15% to 30% depending on the protocol.

The results of all the studies, including reviews, are provided for information in Appendix 2, Table 4 of this opinion (summary tables).

Table 2. Clinical trials in children with acute myeloblastic leukaemia (AML)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Numbers</th>
<th>Population Studied/Inclusion Criteria</th>
<th>Treatment Regimens</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AML-87</strong>&lt;br&gt;Arnaout MK et al. 2000</td>
<td>Prospective, non-comparative study evaluating the efficacy of intensive chemotherapy consisting of six consecutive cycles of four pharmacological dual therapies, with etoposide and cytarabine doses adjusted to plasma concentrations.</td>
<td>N&lt;sub&gt;total&lt;/sub&gt; = 58</td>
<td>Children with newly diagnosed and non-pretreated AML, secondary AML or AML associated with myelodysplastic syndrome, included between 1984 and 1988.</td>
<td>Induction – Cycle 1: IV cytarabine, IV etoposide&lt;br&gt;– Cycle 2: IV cytarabine, IV daunorubicin (50 mg/m&lt;sup&gt;2&lt;/sup&gt; x 2)&lt;br&gt;– Cycle 3: IV etoposide, IV amsacrine&lt;br&gt;Consolidation – Cycle 4: IV etoposide, IV 5-azacitidine&lt;br&gt;– Cycle 5: same as cycle 2&lt;br&gt;– Cycle 6: same as cycle 3</td>
<td>Complete remission: 76% (44/58)&lt;br&gt;Event-free survival at 5 years: 31.0% (±5.9%)&lt;br&gt;Overall survival at 5 years: 41.4% (±6.3%)&lt;br&gt;Deaths: six patients died following the toxic effects of the therapy</td>
</tr>
<tr>
<td><strong>POG 8821</strong>&lt;br&gt;Ravindranath Y. et al. 1996</td>
<td>Randomised, open-label study comparing the efficacy of consolidation with autologous bone marrow transplant versus intensive chemotherapy.</td>
<td>N&lt;sub&gt;Inductions&lt;/sub&gt; = 649&lt;br&gt;– 85% achieved complete remission, N&lt;sub&gt;Remission&lt;/sub&gt; = 552&lt;br&gt;-&gt;232 patients eligible for autologous transplant were randomised, with: – 117 patients in the intensive consolidation group&lt;br&gt;– 115 patients in the autologous transplant group&lt;br&gt;The non-randomised patients were first treated with intensive chemotherapy (n=189) or an allogeneic transplant (n=89).</td>
<td>Children aged under 21 years with non-pretreated AML or isolated myeloid sarcoma, in remission after induction therapy, diagnosed in the United States between 1988 and 1993.</td>
<td>Induction – Course 1: IV daunorubicin (45 mg/m&lt;sup&gt;2&lt;/sup&gt; x 3), IV cytarabine, oral 6-thioguanine&lt;br&gt;– Followed by course 2: high-dose cytarabine&lt;br&gt;Patients randomised if in remission and eligible for transplantation&lt;br&gt;Consolidation – either autologous bone marrow transplant&lt;br&gt;– or intensive chemotherapy (six courses): IV daunorubicin (45 mg/m&lt;sup&gt;2&lt;/sup&gt; x 5), high-dose IV cytarabine, oral 6-thioguanine, IV etoposide, IV azacitidine</td>
<td>→ 82% of the 649 patients treated with induction chemotherapy achieved complete remission.&lt;br&gt;→ Among randomised patients: – event-free survival at 3 years was 36% (±5.8) in the intensive chemotherapy group and 38% (±6.4) in the autologous transplant group (NS, p=0.20)&lt;br&gt;– overall survival at 3 years was 44% (±6.0) in the intensive chemotherapy group and 40% (±6.1) in the autologous transplant group&lt;br&gt;→ Among non-randomised patients, event-free survival at 3 years was 52% (±8.0) in the allogeneic transplant group and 39% (±5.1) in the intensive chemotherapy group.</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Study</td>
<td>Numbers N</td>
<td>Population Studied/ Inclusion Criteria</td>
<td>Treatment Regimens</td>
<td>Endpoints</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| POG 8498      | Non-randomised exploratory study evaluating the combination of high-dose cytarabine and L-asparaginase during the first cycle of intensification / consolidation chemotherapy. All patients in this study were treated with daunorubicin-based induction chemotherapy. | n<sub>total</sub> = 288 – group I: n=140 – group II: n=145 | Children aged under 21 years with non-pretreated AML diagnosed in the United States between 1984 and 1988 | **Induction**  
– Group I: two successive “DAT” courses with IV daunorubicin (45 mg/m² x 3 + x 2), IV cytarabine and oral 6-mercaptopurine  
– Group II: one DAT course followed by one course of high-dose IV cytarabine  
**Intensification/consolidation**  
Cycle 1: either high-dose IV cytarabine x 4 and L-asparaginase (group I) or high-dose IV cytarabine alone x 6 (group II)  
Cycles 2, 3 and 4 the same for both groups: IV etoposide, IV azacitidine, IV prednisone, IV vincristine, IV methotrexate, oral mercaptopurine, IV cytarabine | Remission: 85% of all patients  
Event-free survival at 3 years: 33% for all patients and comparable between groups (NS)  
Group I: 29%±4%  
Group II: 34%±11%  
Disease-free survival at 3 years: comparable between groups (NS)  
Group I: 34%±5%  
Group II: 42%±14% |
08.2 Safety/Adverse effects

8.2.1 PSUR data

The company has provided the five most recent periodic safety update reports (PSURs) covering the period from 1 April 1994 to 31 March 2012. 72 cases were reported, including 62 paediatric cases and 8 cases of foetal exposure. Among these 72 cases, 267 adverse events were reported, including 3 cases of cardiomyopathy, 1 case of congestive heart failure, 1 case of cardiotoxicity, 2 cases of prolonged QT interval, 1 case of sinus bradycardia, 1 heart murmur, 1 case of fatal heart failure and 1 fatal arrhythmia.

In children aged under 15 years, the following adverse events were reported: 1 case of hypertrophic cardiomyopathy, 2 cases of prolonged QT interval, 2 cases of cerebral venous thrombosis, 1 case of cerebellar syndrome with convulsions, 3 cases of posterior reversible encephalopathy syndrome, 1 case of acute invagination of the intestine, 1 case of oesophageal stenosis, 1 case of hepatic veno-occlusive disease, 1 case of secondary AML in a child treated for ALL, 3 cases of bone marrow aplasia, 2 cases of pancytopenia, 8 cases of neutropenia, 1 case of mucosal inflammation, 1 case of generalised oedema associated with sepsis, 1 fungal skin infection and 3 cases of nail discoloration/pigmentation.

08.3 Usage data

26,210 vials of CERUBIDINE 20 mg were sold to hospitals between February 2013 and January 2014 (GERS [Group for the Development and Implementation of Statistics] data).

08.4 Summary & discussion

As in adults, daunorubicin has been an integral part of the chemotherapy protocols used for ALL and AML, primarily in the induction phase, for decades. These treatments have been shown to have:

- a post-induction remission rate that can reach 98% and event-free survival at 10 years of about 70%, depending on the protocol, in children with newly diagnosed ALL;
- a post-induction remission rate of about 60% to 80% and event-free survival at 10 years of 15% to 30% in children with newly diagnosed AML.

No comparative studies have been conducted specifically to evaluate the efficacy and safety of daunorubicin in the treatment of childhood acute leukaemias.

The safety data rely on a limited number of pharmacovigilance reports to quantify the long-term risk of using daunorubicin in children, and primarily concern the risks of cardiomyopathy and secondary malignancies.
**09 THERAPEUTIC USE**\[19,20,21,22\]

**09.1 Acute lymphoblastic leukaemia**

The general regimen used to treat ALL, adjusted for each patient’s risk factors, is:

1. **An induction treatment** (lasting 4 to 6 weeks): the main aim of this is to obtain complete cytological remission with minimal residual disease. This chemotherapy generally combines three cytotoxic substances, vincristine, asparaginase and a corticosteroid, with or without an anthracycline, usually daunorubicin.

2. **A post-induction treatment, also known as consolidation/intensification therapy;** depending on the protocol, this includes 6-mercaptopurine, cyclophosphamide, cytarabine, etoposide and/or an anthracycline.

3. **A maintenance treatment** (lasting about 2 years) combining oral 6-mercaptopurine and oral methotrexate.

4. Neuromeningeal involvement may be prevented with intrathecal injections of methotrexate combined with cytarabine and a corticosteroid (triple intrathecal therapy) or with chemotherapy combining a corticosteroid, high-dose cytarabine and high-dose methotrexate. The role of cranial irradiation in preventing CNS recurrence is limited to a few special cases in patients at very high risk of neuromeningeal recurrence.

5. Haematopoietic stem cell transplantation is rarely indicated in a first remission and only applies to forms with a very poor prognosis (unfavourable mutations, slow response at the start of treatment, infants under 1 year, etc.). In the majority of ALL relapses in children, a haematopoietic stem cell transplant may be considered.

**09.2 Acute myeloblastic leukaemia**

The general regimen used to treat AML is:

1. **An induction treatment;** the main aim of this is to obtain complete cytological remission. This chemotherapy generally combines cytarabine and an anthracycline, most often daunorubicin, with a third cytotoxic drug, etoposide or 6-tioguanine.

2. **A consolidation/intensification treatment,** primarily high-dose cytarabine combined, depending on the protocol, with an anthracycline, 6-tioguanine, etoposide or azacitidine.

3. Neuromeningeal involvement may be prevented with intrathecal injections of methotrexate combined with aracytin and a corticosteroid (triple intrathecal therapy) or with chemotherapy combining a corticosteroid, high-dose cytarabine and high-dose methotrexate.

4. **Allogeneic haematopoietic stem cell transplantation should be considered in young patients with an HLA matched donor in a second remission, and more rarely in a first remission.**

5. **Maintenance treatment** is primarily considered in cases of acute promyelocytic leukaemia.

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\[20\] National Cancer Institute. Childhood Acute Myeloid Leukemia/Other Myeloid Malignancies Treatment. [Accessed 25/02/2014.]

\[21\] National Cancer Institute. Childhood Acute Lymphoblastic Leukemia Treatment. [Accessed 25/02/2014.]


In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual Benefit

- Acute leukaemias are serious and life-threatening diseases.
- This treatment is intended as curative therapy for ALL and AML.
- The efficacy/adverse effects ratio for this medicinal product is high.
- This medicinal product is a first-line therapy.
- Alternative medicinal products exist.

Public health benefit:
Acute lymphoblastic leukaemia and acute myeloblastic leukaemia are serious and life-threatening but rare (orphan) diseases. Their public health burden can be considered as low. The management of rare diseases is a public health need identified in the 2010–2014 National Rare Diseases Plan. Based on the available data, the additional impact of CERUBIDINE on the morbidity, mortality and quality of life of treated patients cannot be quantified. Nonetheless, the role of this medicinal product is recognised through its usage and its contribution to a therapeutic strategy including daunorubicin.

Overall, CERUBIDINE has a small public health benefit in the treatment of acute lymphoblastic leukaemia and acute myeloblastic leukaemia in children.

Taking account of these points, the Committee considers that the actual benefit of CERUBIDINE 20 mg is substantial, as part of a combination chemotherapy regimen, in the treatment of acute lymphoblastic leukaemia and acute myeloblastic leukaemia in children.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indications “in children, as part of a combination chemotherapy regimen: acute lymphoid leukaemia and acute myeloid leukaemia” and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

CERUBIDINE 20 mg does not provide any improvement in actual benefit (level V, non-existent) in the treatment of acute lymphoblastic and myeloblastic leukaemia in children.

010.3 Target population

According to data provided by the Institute for Public Health Surveillance (InVS) in its report on cancers in France, the incidence of acute leukaemia in the paediatric population (0–14 years) was 356 cases of ALL and 90 cases of AML in 2012. The target population for this indication can be estimated at 500 patients.

011 Transparency Committee Recommendations

- Packaging

Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

---

### APPENDIX 1: CERUBIDINE 20 mg, powder for solution for infusion – table comparing previous and new SPC wording

<table>
<thead>
<tr>
<th>Previous SPC wording (14/05/2008)</th>
<th>New SPC wording (from 23/11/2011) amended sections only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.1 Therapeutic indications</strong></td>
<td>4.1 Therapeutic indications</td>
</tr>
<tr>
<td>− Acute leukaemias</td>
<td>− Acute leukaemias</td>
</tr>
<tr>
<td>− Acute transformation of chronic myeloid leukaemia</td>
<td>− Acute transformation of chronic myeloid leukaemia</td>
</tr>
<tr>
<td>− Hodgkin and non-Hodgkin lymphoma</td>
<td>− Hodgkin and non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>In children, as part of a combination chemotherapy regimen:</td>
<td>In children, as part of a combination chemotherapy regimen:</td>
</tr>
<tr>
<td>− Acute lymphoid leukaemia</td>
<td>− Acute lymphoid leukaemia</td>
</tr>
<tr>
<td>− Acute myeloid leukaemia</td>
<td>− Acute myeloid leukaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>4.2 Posology and method of administration</strong></th>
<th><strong>4.2 Posology and method of administration</strong></th>
</tr>
</thead>
</table>
| The dosage varies depending on the indication: 30 to 60 mg/m²/day, intravenously, for 3 to 5 days, at most every 3 to 4 weeks. The total cumulative dose of 600 mg/m² in adults should not be exceeded. Hepatic impairment: reduced dosage (see Precautions for use). | Adults
The dosage varies depending on the indication: 30 to 60 mg/m²/day, intravenously, for 3 to 5 days, at most every 3 to 4 weeks. The total cumulative dose of 600 mg/m² in adults should not be exceeded. Hepatic impairment: reduced dosage (see Precautions for use).
Paediatric population
The dosage is usually calculated based on body surface area and adjusted as needed, depending on clinical response and patients' haematological status; Specific protocols and current guidelines should be consulted for recommended treatments and combinations.
Courses may be administered 3 to 6 weeks apart.
In children aged over 2 years, the risk of cardiotoxicity starts from a cumulative dose of 300 mg/m².
In children aged under 2 years (or with a body surface area under 0.5 m²), the maximum cumulative dose is 10 mg/kg. (…) |

<table>
<thead>
<tr>
<th><strong>5.1 Pharmacodynamic properties</strong></th>
<th><strong>5.1 Pharmacodynamic properties</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines and related substances</td>
<td>Anthracyclines and related substances</td>
</tr>
</tbody>
</table>
Cytotoxic antibiotics and related substances (L: Antineoplastic and immunomodulating agents) | Cytotoxic antibiotics and related substances (L: Antineoplastic and immunomodulating agents) |
Cytostatic anticancer drug from the anthracycline family (antibiotics). This medicine interacts with DNA by intercalation between base pairs, triggering changes in the structure and function of DNA molecules. | Cytostatic anticancer drug from the anthracycline family (antibiotics). This medicine interacts with DNA by intercalation between base pairs, triggering changes in the structure and function of DNA molecules. No controlled studies have been conducted in the paediatric population. |
APPENDIX 2: Summary tables of studies in the paediatric population

Table 3. Results in the paediatric population with acute lymphoblastic leukaemia (ALL)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Protocol Studied</th>
<th>n</th>
<th>Recruitment Period</th>
<th>Median Duration of Follow-Up</th>
<th>Remission Rate</th>
<th>Event-Free Survival pEFS</th>
<th>Overall Survival pOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veerman et al. 2009</td>
<td>DCOG ALL-9</td>
<td>859</td>
<td>1997–2004</td>
<td>6 years</td>
<td>98%</td>
<td>81%**</td>
<td>86%**</td>
</tr>
<tr>
<td></td>
<td>ALL-BFM 83</td>
<td>653</td>
<td></td>
<td>21.7 years</td>
<td>-</td>
<td>65%**</td>
<td>77%*</td>
</tr>
<tr>
<td></td>
<td>ALL-BFM 86</td>
<td>998</td>
<td></td>
<td>18.2 years</td>
<td>-</td>
<td>70%</td>
<td>79%*</td>
</tr>
<tr>
<td></td>
<td>ALL-BFM 90</td>
<td>2178</td>
<td></td>
<td>14.0 years</td>
<td>-</td>
<td>76%*</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>ALL-BFM 95</td>
<td>2169</td>
<td></td>
<td>9.0 years</td>
<td>-</td>
<td>78%*</td>
<td>85%</td>
</tr>
<tr>
<td>Ortega et al. 2001</td>
<td>PETHEMA ALL-69</td>
<td>195</td>
<td>1989–1994</td>
<td>8.6 years</td>
<td>97%</td>
<td>69%*</td>
<td>58%*</td>
</tr>
<tr>
<td>Sackmann-Muriel et al. 1999</td>
<td>Modified ALL-BFM 90</td>
<td>374</td>
<td>1990–1995</td>
<td>5 years</td>
<td>94.4%</td>
<td>64%**</td>
<td>-</td>
</tr>
<tr>
<td>Feig et al. 1996</td>
<td>CCG-1884</td>
<td>92</td>
<td>1990–1992</td>
<td>(relapsed patients)</td>
<td>3 years</td>
<td>69%</td>
<td>10%****</td>
</tr>
<tr>
<td>Steinherz et al. 1993</td>
<td>MSK-NY-II</td>
<td>44</td>
<td>1986–1991</td>
<td>4.5 years</td>
<td>94%</td>
<td>86%***</td>
<td>-</td>
</tr>
<tr>
<td>Eden et al. 1991</td>
<td>UK MRC ALL VIII</td>
<td>630</td>
<td>1980–1984</td>
<td>22.5 years</td>
<td>95%</td>
<td>55%**</td>
<td>57%**</td>
</tr>
</tbody>
</table>

Table 4. Results in the paediatric population with acute myeloblastic leukaemia (AML)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Protocol Studied</th>
<th>n</th>
<th>Recruitment Period</th>
<th>Median Duration of Follow-Up</th>
<th>Remission Rate</th>
<th>Event-Free Survival pEFS</th>
<th>Overall Survival pOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. 2005</td>
<td>CCG 251</td>
<td>485</td>
<td>1979–1983</td>
<td>7.9 years</td>
<td>77%</td>
<td>29%*</td>
<td>31%*</td>
</tr>
<tr>
<td></td>
<td>CCG 213</td>
<td>532</td>
<td>1985–1989</td>
<td>10.9 years</td>
<td>78%</td>
<td>27%*</td>
<td>35%*</td>
</tr>
<tr>
<td></td>
<td>CCG 2891</td>
<td>886</td>
<td>1989–1995</td>
<td>8.9 years</td>
<td>77%</td>
<td>32%*</td>
<td>43%*</td>
</tr>
<tr>
<td>Pession et al. 2005</td>
<td>AIEOP LAM 82</td>
<td>171</td>
<td>1982–1988</td>
<td>12 years</td>
<td>82.4%</td>
<td>29.0%*</td>
<td>36.6%*</td>
</tr>
<tr>
<td></td>
<td>AIEOP LAM 87</td>
<td>151</td>
<td>1987–1993</td>
<td>13 years</td>
<td>82.1%</td>
<td>26.0%*</td>
<td>41.1%*</td>
</tr>
<tr>
<td></td>
<td>AIEOP LAM 87M</td>
<td>77</td>
<td>1989–1993</td>
<td>10 years</td>
<td>64.9%</td>
<td>15.6%*</td>
<td>32.2%*</td>
</tr>
<tr>
<td>Ravindranath Y. et al. 2005</td>
<td>POG 8498</td>
<td>274</td>
<td>1984–1988</td>
<td>-</td>
<td>78.7%</td>
<td>24.1%*</td>
<td>32.6%*</td>
</tr>
<tr>
<td></td>
<td>POG 8821</td>
<td>615</td>
<td>1988–1993</td>
<td>-</td>
<td>77.4%</td>
<td>38.3%*</td>
<td>38.3%*</td>
</tr>
<tr>
<td></td>
<td>POG 8101</td>
<td>257</td>
<td>1981–1986</td>
<td>-</td>
<td>81.8%</td>
<td>16.3%*</td>
<td>22.9%*</td>
</tr>
<tr>
<td>Arnaout MK et al. 2000</td>
<td>AML-87</td>
<td>58</td>
<td>1984–1988</td>
<td>6.4 years</td>
<td>76%</td>
<td>31.0%**</td>
<td>41.4%**</td>
</tr>
<tr>
<td>Ravindranath Y. et al. 1991</td>
<td>POG 8498</td>
<td>288</td>
<td>1984–1988</td>
<td>-</td>
<td>85%</td>
<td>33%****</td>
<td>-</td>
</tr>
<tr>
<td>Creutzig et al. 1990</td>
<td>AML-BFM 78</td>
<td>151</td>
<td>1978–1982</td>
<td>8.5 years</td>
<td>80%</td>
<td>37%****</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>AML-BFM 83</td>
<td>182</td>
<td>1982–1986</td>
<td>4.5 years</td>
<td>80%</td>
<td>49%****</td>
<td>-</td>
</tr>
</tbody>
</table>

Estimated survival: * at 10 years; ** at 5 years; *** at 4 years; **** at 3 years; ***** at 6 years