HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

6 February 2013

DACOGEN 50 mg, powder for concentrate for solution for infusion

B/1 vial (CIP code: 2670383)

Applicant: JANSSEN-CILAG

INN	decitabine
ATC Code (2012)	L01BC08 (Pyrimidine analogues)
Reason for the review	**Inclusion**
List(s) concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"DACOGEN is indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy."**

Actual Benefit	The actual benefit is substantial in the indication in the Marketing Authorisation.
Improvement in Actual Benefit	In view of: - an observed therapeutic effect primarily on complete remission, without a demonstrated impact on overall survival, and - the restriction in treatment options at this stage of the disease and that may be mainly represented by supportive care alone, the Transparency Committee considers that DACOGEN provides a minor improvement in actual benefit (level IV) in the treatment strategy of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.
Therapeutic use	Regarding conventional treatments that are available, DACOGEN is a first-line therapy in the treatment of acute myeloid leukaemia, for patients aged 65 years and above, who are not candidates for standard induction chemotherapy with benefits primarily shown for complete remission, but without a demonstrated impact on overall survival.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (European centralised procedure)	Date of Marketing Authorisation (centralised procedure): 20th of September 2012
Prescribing and dispensing conditions / special status	List I Medicine for hospital prescription only. Prescription restricted to haematology specialists or doctors with blood disorder training. Medicine requiring special monitoring during treatment. Orphan medicinal product.

ATC Classification	2012	
	L	: Antineoplastic and immunomodulating agents
	L01	: Antineoplastic agents
	L01B	: Antimetabolites
	L01BC	: Pyrimidine analogues
	L01XE11	: decitabine

02 THERAPEUTIC INDICATION(S)

“DACOGEN is indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.”

03 DOSAGE

“In a treatment cycle, DACOGEN is administered at a dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e. a total of 5 doses per treatment cycle).
The total daily dose must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2. If a dose is missed, treatment should be resumed as soon as possible. The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial remission may take longer than 4 cycles to be obtained. Treatment may be continued as long as the patient shows response, continues to benefit or exhibits stable disease, i.e. in the absence of overt progression.
If after 4 cycles, the patient's haematological values (e.g., platelet counts or absolute neutrophil count), have not returned to pre-treatment levels or if disease progression occurs (peripheral blast counts are increasing or bone marrow blast counts are worsening), the patient may be considered to be a non-responder and alternative therapeutic options to DACOGEN should be considered.
Pre-medication for the prevention of nausea and vomiting is not routinely recommended but may be administered if required.”

04 THERAPEUTIC NEED[1,2,3]

Acute myeloid leukaemia (AML) is a heterogeneous group of malignant haemopathies characterised by clonal proliferation of abnormal myeloid precursors and impairment of normal haematopoiesis. The WHO classification uses as a diagnostic threshold the bone marrow infiltration by more than 20% of non-lymphoid blasts.
The incidence of AML in adults is between 5 and 8/100,000 per year in Europe; incidence increases with age, especially over 50 years. The mortality rate is 4 to 6/100,000 per year. The median age at diagnosis is 65 years.

Treatment for acute myeloid leukaemia (AML) is different depending on the age and general health of the population concerned:
- for patients under 60 years, the therapeutic aim of AML treatment is curative. It is based on intensive chemotherapy lasting approximately 6 months, including a reference induction regimen combining cytarabine (100-200 mg/m^2 or more) and an anthracycline, which will result in several weeks of myelosuppression requiring admission to a hospital isolation unit.
After the induction phase, a consolidation phase with chemotherapy or a haematopoietic stem cell transplant, depending on the cytogenetic risk, will be implemented to prevent a relapse. Complete remission is a necessary preliminary for long-term survival. There is a significant risk of relapse, but a patient who is still in complete remission after more than five years may be considered as cured.
- for patients over 60 years, it is recommended to establish during diagnosis if there are any unfavourable prognosis factors: frailty, co-morbidities, unfavourable cytogenetics and secondary AML.

Induction chemotherapy, similar to that used for younger patients, will only be used if the risk of toxicity of the chemotherapy and the risk of resistance are not considered to be excessive. Patients presenting with an ECOG score greater than 2, aged over 80 years, and with signs of infection, co-morbidities and/or unfavourable cytogenetics are not able to receive this type of chemotherapy.
In Europe and in the United States, low doses of cytarabine are the usual first-line treatment used in the elderly who are not candidates for treatment with cytarabine- and anthracycline-based induction chemotherapy. A palliative treatment with hydroxyurea or 6-mercaptopurine alongside symptomatic treatment may be administered to control leukocytosis.

[1]Société Française d'Hématologie (SFH) [French Society of Haematology] SFH reference 2009 [online]. 2009. Available: URL: http://sfh.hematologie.net/hematolo/UserFiles/File/REFERENTIEL%20COMPLET%20VERSION%20FINALE%20SFH20082009%281%29.pdf
[2] EPAR DACOGEN (2012)
[3] Acute Myeloid Leukemia NCCN 2012

05 RELEVANT COMPARATOR MEDICINES

05.1 Medicinal products

ARACYTINE (cytarabine) used in subcutaneous injections at low doses.

According to the FAB (Franco-American-British) classification, AML is defined as a ≥ 30% blasts count, while the WHO uses a threshold of ≥ 20%. VIDAZA is only indicated for myelodysplastic syndromes (MDS) (<30% of blasts with myelodysplasia). Even though some experts agree to the possible off-label use of VIDAZA for AML, this is not a comparator medicine for DACOGEN, which is only indicated for use for AML (≥30% of blasts according to FAB classification). Studies that evaluated VIDAZA are based on data for patients who have MDS.

◗ Conclusion

The relevant comparator medicine with Marketing Authorisation is cytarabine at low doses.

06 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	TREATMENT	
	YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
USA	Yes but in a different indication (myelodysplastic syndrome)	NA
EU	No (procedures in progress)	

07 ANALYSIS OF AVAILABLE DATA

The dossier requesting inclusion includes:
- a phase II non-comparative study: DACO-17
- a phase III pivotal study: DACO-16.

07.1 Efficacy

DACO-17 Study
A non-comparative phase II study of 55 patients, age > 60 years with acute myeloid leukaemia (AML) based on the WHO classification. The primary efficacy endpoint of the study was complete remission rate (CR)[4] and the secondary endpoint was overall survival. The evaluation was carried out by an independent expert review board. Decitabine (DACOGEN) was administered via intravenous (IV) infusion over 1 hour at a dose of 20 mg/m² once daily for 5 consecutive days and repeated every 4 weeks. In the intention to treat analysis, a CR rate of 23.6% (95% CI: [13.2 – 37]) was observed in 13/55 of the patients treated with decitabine. The median time to CR was 4.1 months, and the median CR duration was 18.2 months. The median overall survival of the intention to treat population was 7.6 months (95% CI: [5.7 - 11.5]).

DACO-16 Study[5]
A randomised, open-label phase III study that evaluated the efficacy and safety of decitabine versus a conventional treatment (cytarabine at low doses or supportive care) in patients aged 65 years and more, with acute myeloid leukaemia, who were not candidates for standard induction chemotherapy.

Before randomisation, on physician's advice, patients were asked their preference between treatment with a low dose of cytarabine or supportive care; however, this was only for randomisation into the conventional treatment group.
Patients were randomised at a 1:1 ratio into one of the following two groups:

- decitabine group: patients received an IV infusion over one hour of 20 mg/m² of body area per day, for 5 consecutive days, per 28 day cycle;
- conventional treatment group: depending on their choice (selected prior to randomisation), patients received,:
    - either cytarabine, administered at a dose of 20 mg/m² via subcutaneous injection once daily for 10 days per 28 day cycle,
    - or only supportive care: antibiotics, antifungal treatments, transfusions, plasma, enteral or parenteral feeding, radiation treatment with the aim of controlling pain, erythropoietin, etc.

Randomisation of patients was stratified based on the following criteria, known as being prognosis factors for AML: [6]

- ECOG performance score: 0 or 1 versus 2;
- age: 65-70 years versus older than 70 years;

[4] Defined as follows:
- percentage of medullary blasts <5%;
- number of nucleated cells ≥ 200 (and absence of blasts with Auer bodies or persistence of extra-medullary disease);
- Neutrophil count > 1 000/µl;
- platelet count ≥ 100 000/µl;
- The patient must not have received a transfusion for at least one week before each evaluation.

[5] Kantarjian H., Thomas X., et al. Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia. Journal of Clinical Oncology; 2012 Jul 20; 30 (21): 2670-7.

[6] Wheatley K, Brookes CL, Howman AJ. Et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML 14 trials. British J of Hematol 2009; 145: 598-605.

- cytogenetic risk: high risk versus intermediate risk.

The protocol allowed for the fact that patients receiving either decitabine or low dose cytarabine could also receive supportive care.
Patients were treated up to the point of relapse, disease progression, death, unacceptable toxicity, an absence of clinical benefit, an intercurrent illness affecting the treatment or at the request of the patient or the physician.

The primary efficacy endpoint was overall survival, defined as the time between randomisation and death of the patient from any cause.
The secondary endpoints were:
- complete morphological remission rate (CR, evaluated by a board of independent experts) and complete remission with partial platelets recovery (CRp) (see definitions on Annex 1);
- incidence and severity of toxicity.

The main exploratory endpoints were as follows:
- event-free survival: event-free survival was defined as the time between randomisation and the occurrence of an event or the last available follow-up. An event was defined as failure of treatment (discontinuation of treatment due to death, disease progression, or an adverse effect linked to treatment), relapse following complete remission, death or the last available follow-up.
- progression-free survival: progression-free survival was defined as the time between randomisation and disease-progression or death.
- relapse-free survival: relapse-free survival was only applicable for patients who presented a complete remission. This was defined as the time between remission and the first of any of the following events: relapse, death or lost to follow-up.

Inclusion criteria:

- AML, according to WHO classification (≥20% of medullary blasts), de novo or secondary, newly diagnosed and confirmed histologically
- age ≥ 65 years
- a high or intermediate cytogenetic risk according to the Southwest Oncology Group
- a WHO / ECOG performance score: 0 to 2
- the following laboratory results:
    - haematology: leukocytes ≤ 40 000/mm
    - hepatology: bilirubin ≤1.5 x ULN (upper limit of normal), ASAT or ALAT ≤2.5 x ULN
    - nephrology: creatinine clearance (according to Cockroft and Gault formula) ≥ 40 ml/min
- life expectancy of at least 12 weeks.

Exclusion criteria:

- acute promyelocytic leukaemia (M3 classification)
- karyotype abnormalities: t(8;21), chromosome 16 or t(15;17) abnormality
- proven leukaemia affecting the central nervous system
- presence of another systemic malignant tumour
- unstable angina or class 3 or 4 congestive heart failure according to the New York Heart Association (NYHA)
- chronic respiratory disease requiring the daily use of oxygen
- non-aspirable bone marrow
- previous chemotherapy treatment (with the exception of hydroxyurea), including azacitidine, cytarabine or DACOGEN for any type of myeloid disorder
- treatment with an experimental medicine during the 4 weeks of randomisation
- to be considered as a potential candidate for a haematopoietic stem cell transplant during the 12-week post-randomisation period
- treatment with radiotherapy for an extra-medullary disorder in the 2 weeks prior to randomisation
- medical or psychological disorders incompatible with the study (at the discretion of the study investigator)
- a co-morbidity resulting in an organic impairment not linked to leukaemia

- uncontrolled, active infection requiring the use of antibiotics
- proven HIV infection

Statistical analysis
The primary efficacy endpoint of this study was overall survival.
The study was designed to detect a reduction of 25% in the risk of death (Hazard Ratio for overall survival = 0.75) with a power of at least 80%. The sample size was calculated using the hypothesis of a median survival of 6 months in the conventional treatment arms and 8 months in the DACOGEN arm, an α risk of 0.05 and the performance of a bilateral test.
Inclusion of 480 patients (240 per treatment arm) should enable a reduction of 25% in the expected risk of mortality to be detected after 385 events had been observed. A 15-month inclusion period was proposed in order to include the correct number of patients required.
For analysis of overall survival, patients still alive at the date of closure of the database were recorded on the last date of known life.
A Kaplan-Meier analysis enabled the distribution and median overall survival to be estimated. A stratified log-rank test was used to make statistical comparisons between the two treatment arms. Stratification enabled variability in response due to covariates to be reduced. Stratification factors were age (<70, ≥70 years), cytogenetic risk (intermediate risk vs. high risk) and the ECOG performance score (0-1 vs. 2). Estimations of the Hazard Ratio and its confidence interval were obtained from a Cox model, stratified on age, cytogenetic risk and the ECOG performance score.
After adjusting for the alpha risk for the two interim analyses, the significance alpha risk for the primary analysis (28 October 2009) was set at 0.0462 (bilateral test).

Results:
A total of 485 patients were randomised: 242 patients in the decitabine group and 243 patients in the conventional treatment group. The median age of patients was 73 years.
The majority of patients (74.3%) presented with an ECOG score of 0 or 1 (full independence or only reduced during exercise).
Approximately two thirds (64.3%) of patients presented with de novo AML, i.e. with no known etiology. The median time since diagnosis was 15 days before inclusion in the study.
In the conventional treatment group, 28 patients received supportive care and 215 (88%) received low dose cytarabine.

Table 1: **DACO-16 study – Baseline characteristics of patients (ITT population)**

Characteristics	Decitabine N = 242	Conventional treatments N = 243
Age, N	242	243
Mean, years (SD)	73.14 (5.24)	73.53 (5.67)
Median, years	73.0	73.0
Interval (min; max), years	64; 89	64; 91
< 65 years, n (%)	3 (1.2%)	1 (0.4%)
65 – 69 years, n (%)	68 (28.1%)	69 (28.4%)
70 – 74 years, n (%)	76 (31.4%)	74 (30.5%)
75 – 79 years, n (%)	65 (26.9%)	57 (23.5%)
≥ 80 years, n (%)	30 (12.4%)	42 (17.3%)
Time since AML diagnosis (days), N	241	239
Mean, days (SD)	19.05 (25.08)	27.41 (46.37)
Median, days	14.0	15.0
Interval (min; max), days	3.0; 346.0	0; 398.0
AML type, N (%)	242	243
De novo	155 (64.0%)	157 (64.6%)
Secondary	87 (36.0%)	84 (34.6%)
NA	0	2 (0.8%)
Origin of secondary AML, N	87	84
Myelodysplastic syndrome	59 (67.8%)	74 (88.1%)
Myelodysplastic disorder	16 (18.4%)	8 (9.5%)
Proven exposure to a risk factor	12 (13.8%)	2 (2.4%)
Medullary blasts, N (%)	241	241
<20	4 (1.7%)	8 (3.3%)
20-30	65 (27.0%)	58 (24.1%)
>30-50	67 (27.8%)	74 (30.7%)
>50	105 (43.6%)	101 (41.9%)
Mean (SD)	50.31 (23.83)	49.58 (23.45)
Median	46.6	45.0
Interval (min; max)	3; 100	0; 100
ECOG performance score, N	242	243
0	42 (17.4%)	47 (19.3%)
1	140 (57.9%)	131 (53.9%)
2	60 (24.8%)	65 (26.7%)
Cytogenetic risk, N	241	242
Intermediate	152 (63.1%)	154 (63.6%)
High	87 (36.1%)	87 (36.0%)
NA	2 (0.8%)	0
NK	0	1 (0.4%)
Patients presenting with at least one co-morbidity	196 (81.0%)	199 (81.9%)
1 co-morbidity	93 (38.4%)	87 (35.8%)
2 co-morbidities	70 (28.9%)	73 (30.0%)
3 co-morbidities or more	33 (13.6%)	39 (16,0%)

SD: standard deviation or root mean square deviation; NA: Not Applicable; NK: Not known

Results for the primary endpoint: overall survival

In the primary analysis (carried out in October 2009) after 396 deaths, there was no difference in the median overall survival between the two groups: 7.7 months, 95% CI: [6.2 - 9.2] in the decitabine group versus 5.0 months, 95% CI: [4.3 - 6.3] in the conventional treatment group. (HR = 0.85, 95% CI: [0.69 - 1.04]; p = 0.1079).

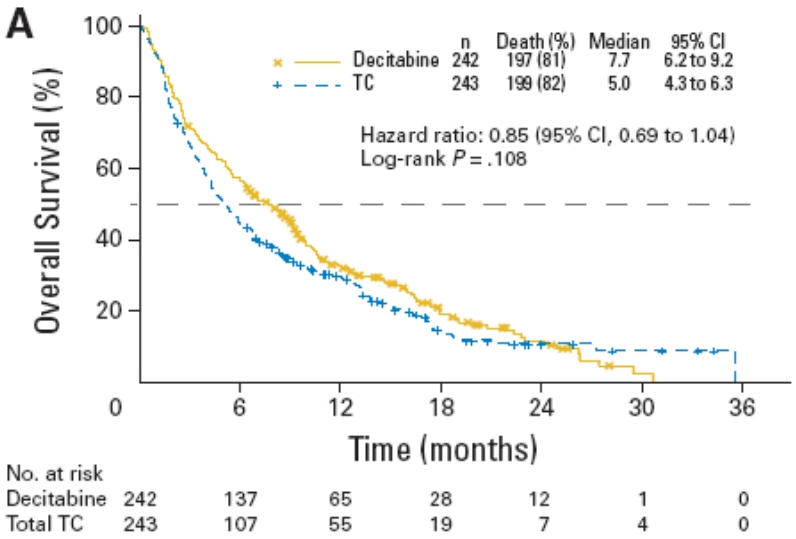
In this analysis, the median follow-up for patients was 7.0 months [min: 0.3 – max: 3.7] in the decitabine group versus 5.0 months [min: 0.2 – max: 35.6] in the conventional treatments group.

Table 2: DACO-16 study – Results for the primary endpoint (ITT population; 28 October 2009 - after 396 deaths)

	Decitabine N = 242	Conventional treatments N = 243
Randomised patients, ITT o Patients recorded, n (%) o Still alive, n (%) o Lost to follow-up, n (%)	242 45 (18.6%) 44 (18.2%) 1 (0.4%)	243 44 (18.1%) 43 (17.7%) 1 (0.4%)
Overall survival (months)[a] o 25th percentile [95% CI] o **Median [95% CI]** o 75th percentile [95% CI]	 2.6 [2.1 - 3.4] **7.7 [6.2 - 9.2]** 16.3 [12.7 - 17.9]	 2.0 [1.7 - 2.7] **5.0 [4.3 - 6.3]** 13.3 [10.4 - 16.3]
Survival rate [95% CI] o Survival rate at 6 months o Survival rate at 12 months o Survival rate at 18 months	 56.9% [50.4 - 62.9] 32.6% [26.6 - 38.8] 19.1% [13.8 - 25.0]	 44.3% [38.0 - 50.4] 29.4% [23.6 - 35.3] 14.6% [9.9 - 20.2]
p*	0.1079	
Hazard ratio [95% CI]	0.85 [0.69 - 1.04]	

[a]: the survival time is the time between randomisation and death from any cause; the survival time for patients who had not died at the time of the analysis was recorded on the date of the last event or lost to follow-up ; *log-rank stratified by ECOG stage, age and cytogenetic risk

Figure 1: DACO-16 study – Kaplan-Meier curves for overall survival (primary endpoint; 28 October 2009)



The results for the sensitivity analysis, not stratified on age, cytogenetic risk or ECOG score, were equivalent to those for the stratified analysis.

A sensitivity analysis recording patients who received treatment with intensive chemotherapy, azacitidine or decitabine following discontinuation of the study treatment, was performed in order to ascertain the individual effect of the study treatments. Based on the 2009 analysis, 75 patients received one of these treatments following discontinuation of the study treatment: 31 in the decitabine arm and 44 in the conventional treatment arm. Analysis after recording suggested a HR value of 0.80 [95% CI: 0.64 - 0.99]), with a median survival of 5.3 months 95% CI: [4.3 - 6.7] in the

conventional treatments group versus 8.5 months 95% CI: [6.5 - 9.5] in the decitabine group (log-rank test p = 0.0437).

A post-hoc analysis, carried out after an additional follow-up period of one year suggested a difference of 2.7 months in the overall survival between the two groups of patients, in favour of decitabine: 7.7 versus 5.0; HR = 0.82, 95% CI: [0.68 – 0.99]; log-rank test p = 0.0373.

Results for the secondary endpoints, carried out in the primary analysis, are given for information:
- the rates of complete morphological remission and complete remission with partial recovery of platelet count were 17.8% in the decitabine group versus 7.8% in the conventional treatments group.
- the median event-free survival was 3.5 months in the decitabine group versus 2.1 months in the comparator group.
- the median time to achieve the best response was 4.3 months in the decitabine group and 3.7 months in the conventional treatments group. The duration of response was 8.3 months in the decitabine group and 12.9 months in the conventional treatments group.
- progression-free survival was 3.7 months in the decitabine group versus 2.1 months in the comparator group.

07.2 Safety/Adverse effects

The frequency of discontinuation of treatment for an adverse event was 6% in the decitabine group, 0% in the supportive care sub-group and 8% in the low-dose cytarabine sub-group. This frequency of discontinuation of treatment in the decitabine group rises from 6% to 37% (and from 8% to 47% in the low-dose cytarabine group) if all studies carried out for AML are included.[7]
By including all studies carried out on AML, grade 3 or 4 adverse events are observed in 73% of patients in the decitabine group, 34% of patients in the supportive care sub-group and 63% in the low-dose cytarabine sub-group. These events mainly involve infections (decitabine: 47%, supportive care: 28% and cytarabine: 30%) and haematological and lymphatic system disorders (decitabine: 35%, supportive care: 0%; cytarabine: 28%).
The main serious adverse events were febrile neutropenia (decitabine: 24%, supportive care: 0%; cytarabine: 15%), thrombocytopenia (decitabine: 9%, supportive care: 0%; cytarabine: 5%) and pneumonia (decitabine: 18%, supportive care: 10%; cytarabine: 14%).

07.3 Summary & discussion

A randomised, open-label phase III study evaluated the efficacy and safety of decitabine versus a conventional treatment (cytarabine at low doses or supportive care) in patients aged 65 years and above, with acute myeloid leukaemia (AML), who were not candidates for standard induction chemotherapy (advanced age and/or presence of co-morbidities) with high dose cytarabine and anthracyclines.
The primary efficacy endpoint was overall survival, defined as the time between randomisation and death of the patient from any cause.

A total of 485 patients, with a median age of 73 years were randomised: 242 patients in the decitabine group and 243 patients in the conventional treatment group.
The majority (88%) of patients in the conventional treatment group received low-dose cytarabine.
Approximately three quarters of patients (74,3%) had an ECOG score of 0 or 1 (full independence or only reduced during exercise).
Approximately two thirds (64.3%) of patients presented with de novo AML, i.e. with no known etiology. The median time since diagnosis was 15 days before inclusion in the study.

[7] EPAR, p74

The primary analysis carried out after 396 deaths (October 2009), showed a median overall survival not different (HR = 0.85 95% CI: [0.69 - 1.04]; p = 0.1079) between the decitabine group (7.7 months [6.2 - 9.2]) and the conventional treatment group (5.0 months [4,3 - 6,3]).
A post-hoc analysis carried out after an additional follow-up period of one year suggested a difference of 2.7 months in the median overall survival between the two groups of patients in favour of decitabine: 7.7 versus 5.0; HR = 0.82, 95% CI: [0.68 – 0.99]; log-rank test p = 0.0373.
Results for the secondary endpoints carried out in the primary analysis showed:
- a rate of complete morphological remission and complete remission with partial recovery of platelet count of 17.8% in the decitabine group versus 7.8% in the conventional treatments group.
- a median time to achieve the best response of 4.3 months in the decitabine group and 3.7 months in the conventional treatments group. The duration of response was 8.3 months in the decitabine group and 12.9 months in the conventional treatments group.
- a median event-free survival of 3.5 months in the decitabine group versus 2.1 months in the comparator group.
- a progression-free survival of 3.7 months in the decitabine group versus 2.1 months in the comparator group.

The toxicity of decitabine mainly resulted in infections: febrile neutropenia and pneumonia noted as serious adverse events in approximately 20% of cases (0% and 10% respectively in the supportive care group and 15% and 14% respectively in the cytarabine group).

08 THERAPEUTIC USE

In Europe and in the United States, low dose-cytarabine is the usual first-line treatment for AML in very elderly patients who are considered as being unable to cope with an intensive treatment (WHO >2 or serious co-morbidities) with high doses of cytarabine and anthracyclines. Palliative treatment with hydroxyurea or 6-mercaptopurine in combination with symptomatic treatment may also be given to control leukocytosis.
Regarding conventional treatments that are available and given the benefit shown for complete remission, which is the short-term aim investigated, DACOGEN is a first-line treatment in the management of acute myeloid leukaemia, for patients aged 65 years and above, who are not candidates for standard induction chemotherapy.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

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

09.1 Actual benefit

- Acute myeloid leukaemia is a serious, life-threatening disease.
- This proprietary medicinal product is intended as a curative therapy, specific for acute leukaemia.
- The efficacy/adverse effects ratio is high.
- There are few alternative medicinal products.
- This medicinal product is a first-line treatment.

- Public health benefit:

  The public health burden of acute myeloblastic leukaemia (AML) can be regarded as low (due to the rareness of the condition).

  Improvement in the treatment of AML is a public health need which is an established priority (Rare Disease Plan, Cancer Plan).

  According to clinical data available [study versus conventional treatments (cytarabine or supportive care) suggestive of a small improvement in overall survival], the impact of DACOGEN on morbidity, mortality and quality of life compared with current treatment strategies is not yet established.

  As a result, the proprietary medicinal product DACOGEN is not expected to meet the identified public health need.

  Furthermore, there is no data available on its impact on the organisation of care.

  Consequently, DACOGEN is not expected to benefit public health.

Taking account of these points, the Committee considers that the actual benefit of DACOGEN is substantial in the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

09.2 Improvement in actual benefit (IAB)

In view of:

- a therapeutic effect noted mainly on complete remission, without a demonstrated impact on overall survival, and
- the restriction in treatment options at this stage of the disease, which may be mainly represented by supportive care alone,

the Transparency Committee considers that DACOGEN provides a minor improvement in actual benefit (IAB IV) in the treatment strategy of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

09.3 Target population

The target population of DACOGEN corresponds to patients with acute myeloid leukaemia, aged 65 years and above and who are not candidates for standard induction chemotherapy.
In France, the number of patients aged 65 years and above presenting with acute leukaemia in 2011 has been estimated as 1,864 patients[8]. Acute myeloid leukaemia is the most common form of leukaemia in adults. According to experts, it represents 70% to 80% of cases of leukaemia in adults, which corresponds to 1,500 patients over 65 years presenting with acute myeloid leukaemia (AML).
The incidence of AML in adults is between 5 and 8 per 100,000 people per year in Europe.[9] Incidence increases with age, especially after 50 years, giving a figure of 9.7 per 100,000 between 65 years and 69 years which rises to 21.6 per 100,000 people in patients aged 85 years and above.[10] Relating this incidence to the French population[11] enables the number of cases seen in patients aged 65 or above to be estimated as 1,763 per year.
The target population for DACOGEN is based on patients who are not candidates for standard induction chemotherapy. The proportion of elderly patients who are not candidates for standard induction chemotherapy may be estimated, in France, as 40%.[12]
The target population for DACOGEN is therefore approximately 700 patients per year.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee recommends the inclusion of DACOGEN on the list of medicines approved for hospital use in the indication "treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy" and at the dose in the Marketing Authorisation.

Packaging

It is appropriate for the prescription conditions according to the indication, the dose and the treatment duration.

[8] INVS- INCa. Projection of the incidence and mortality by cancer in France in 2011. June 2011
[9] SFH [French Society of Haematology] reference 2009
[10] SEER Cancer Statistics Review 1975 – 2006; http://seer.cancer.gov/csr/1975_2006/browse_csr.php
[11] INSEE : http://www.recensement-2009.insee.fr/tableauxDetailles.action?zoneSearchField=FRANCE&codeZone=1-FE&idTheme=12&idTableauDetaille=51&niveauDetail=1
[12] Vey N et al. The benefit of induction chemotherapy in patients age ≥ 75 years. A retrospective study in 110 patients from a single institution. CANCER. 2004; 101 (2): 325-331.

Appendix 1: Definition of evaluation criteria for DACO-16 Study

Response	Evaluation criteria for the clinical investigators	Evaluation criteria for the independent expert review board
Complete morphological remission (CR)	- Level of medullary blasts <5%; - Number of nucleated cells ≥ 200 (and absence of blasts with Auer bodies or persistence of extra-medullary disease); - Neutrophil count > 1 000/µl; - Platelet count ≥ 100 000/µl; - The patient must not have received a transfusion for at least one week before each evaluation. Absence of minimum duration to confirm this state.	- Level of medullary blasts <5%; - Number of nucleated cells ≥ 200 (and absence of blasts with Auer bodies or persistence of extra-medullary disease); - Neutrophil count > 1 000/µl; - Platelet count ≥ 100 000/µl; - The patient must not have received a transfusion for at least one week before each evaluation. Absence of minimum duration to confirm this state.
Complete morphological remission with incomplete recovery of platelets (CRp)	Idem complete morphological remission except for obligatory platelet count ≥100 000/µl.	Idem complete morphological remission except for obligatory platelet count ≥100 000/µl.

Disease progression	<u>During the first cycle:</u> Evaluation based on peripheral blood count, evidence of a new extra-medullary disease and/or the clinical judgement of the study investigator: - If the number of circulating blasts has increased by more than 50% compared with the pre-treatment value during the first cycle, patients should leave the study due to disease progression; - Evaluation of the bone marrow was recommended to confirm disease progression in patients with an increase of more than 50% in circulating blasts. Patients presenting with an increase of more than 25% compared with pre-treatment levels of medullary blasts were also considered as having progression. <u>During subsequent cycles:</u> disease progression was based on: - an increase in the number of circulating blasts by more than 50% compared with the baseline value evaluated through a bone marrow aspiration biopsy taken 7 days before one cycle out of two from the third cycle (and at the end of the first and third cycle after complete remission, if required); - or on clinical signs of evidence of a new extra-medullary disease; - or on the judgement of the investigator.	<u>During the first cycle:</u> Evaluation based on peripheral blood count, evidence of a new extra-medullary disease and/or the clinical judgement of the study investigator: - If the number of circulating blasts has increased by more than 50% compared with the pre-treatment value during the first cycle, the patient was considered as having disease progression if a bone marrow biopsy was not performed. If a bone marrow biopsy had been carried out during the first cycle or before the start of the second cycle, then an increase of more than 25% compared with the baseline value of the number of medullary blasts was considered as disease progression. <u>During subsequent cycles:</u> disease progression was defined as an increase in the number of circulating blasts by more than 50% compared with baseline value or after clinical signs of an new extra-medullary disease or on the clinical judgement of the study investigator. <u>Determination of disease progression for patients in complete remission or presenting with a stable disease</u>: Progression based on the number of circulating blasts, evidence of a new extra-medullary leukaemia and/or on the clinical opinion of independent experts. If the number of circulating blasts increases by more than 50% compared with the lowest level, the patient is considered as having disease progression in the absence of a bone marrow biopsy. If a bone marrow biopsy has been carried out, an increase of more than 25% in the number of medullary blasts compared with the lowest level is considered as disease progression.
Recurrence/morphological relapse/ relapse after complete remission	Reappearance of circulating leukemic blasts or a level of medullary blasts ≥ 5% not attributable to another cause. In the absence of circulating blasts but with 5% to 20% of medullary blasts, a bone marrow biopsy should be taken at least one week later to confirm relapse.	Relapse for patients in complete remission is defined as the reappearance of circulating leukemic blasts or of more than 5% of medullary blasts not attributable to another cause (e.g. the regrowth of bone marrow after consolidation therapy). The appearance of new dysplastic changes, the reappearance or development of an extra-medullary disease proven through cytology indicates a relapse. Genetic relapse was characterised by the reappearance of cytogenetic abnormalities.