European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR EVOLTRA

International Nonproprietary Name:
Clofarabine

Procedure No. EMEA/H/C/613/II/01

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the application, with all information of a commercially confidential nature deleted. It may not include all available information on the product in the event that the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application. It should therefore be read in conjunction with the "Questions and Answers" document on the withdrawal of the application, which provides an overview of all available information at the time of the Applicant's withdrawal.

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I CHMP RECOMMENDATION PRIOR TO THE WITHDRAWAL

Based on the review of the data on safety and efficacy, the CHMP considered that the variation application EMEA/H/C/613/II/01 for Evoltra (clofarabine), currently authorised for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients, to include a new indication "*treatment of acute myeloid leukaemia (AML) in elderly patients who have one or more of the following: adverse cytogenetics, secondary AML, ≥ 70 years old or significant co-morbidities and are therefore not considered suitable for intensive chemotherapy. Safety and efficacy have been assessed in studies of patients ≥ 65 years old (see section 5.1)*"

is not approvable since major objections have been identified which preclude a recommendation for such variation and recommend that the variation to the terms of the Marketing Authorisation should be refused at the present time.

II EXECUTIVE SUMMARY

Scope of the variation

On 23 February 2006, the CHMP adopted a positive opinion for the Marketing Authorisation of Evoltra in the treatment of paediatric patients (≤ 21 years old) with acute lymphoblastic leukaemia (ALL) who are in second or subsequent relapse or are refractory.

The original submission also sought approval for the treatment of paediatric patients (≤ 21 years old) with acute myeloid leukaemia (AML) who are in first or subsequent relapse or are refractory. During the evaluation procedure, the applicant withdrew the claim for this indication as the CHMP considered that the clinical documentation provided was not sufficient to establish the clinical efficacy of clofarabine in this patient population. In particular, although one patient achieved a complete response in the absence of total platelet recovery (CRp), no complete response (CR) was observed with clofarabine in the interim results submitted for the non-randomised study CLO-222. The applicant decided to withdraw the paediatric AML indication from the initial marketing authorisation application after further review of the efficacy data collected from study CLO-222, but informed the CHMP that they were planning a future resubmission for the treatment of AML pending the results of an ongoing study in adult patients.

This type II variation is to extend the current therapeutic indication to include the following new indication:
"Treatment of acute myeloid leukaemia (AML) in elderly patients who have one or more of the following: adverse cytogenetics, secondary AML, ≥ 70 years old or significant co-morbidities and are therefore not considered suitable for intensive chemotherapy. Safety and efficacy have been assessed in studies of patients ≥ 65 years old (see section 5.1)."
There were a number of consequential changes to different sections of the SPC as the proposed extension to the current indication is for a different type of leukaemia and the patient population is different.

Acute myeloid leukaemia (AML) is the most common type of acute leukaemia. The annual incidence rates in Europe range from 2 to 4 per 100,000. The incidence of AML increases with age and is almost 10 times greater among people 65 years of age and older than among those younger than 65 years of age. If left untreated, AML usually results in death within a few months of diagnosis. Conventional cytotoxic chemotherapy for AML can be associated with serious adverse effects and, as a result, can often not be tolerated by older patients.
The current standard of care for these patients is either low dose cytarabine (LDAC) or hydroxyurea. LDAC has been shown to be more effective in this population, but it only achieves a complete response rate of 20% and a median survival of 3 months. In addition, elderly patients with poor prognostic factors, adverse cytogenetics, secondary AML or coexistent morbidity, respond poorly to any treatment and have a high mortality rate.

III SCIENTIFIC DISCUSSION

Pharmacokinetics

In support of the updated section 5.2 of the SPC, pharmacokinetic data were collected from seven clinical studies in patients treated with clofarabine: five from the previous submission and two additional studies: CLO-151 and BIOV-111.

Regarding the ongoing study CLO-151, the applicant provided an interim report, which did not include a PK analysis.
The submitted PK data referred to an oral communication (Abstract submitted on 22 Dec 2003 by Cunningham & al ; ref.16 in the summary of study CLO-151).
Comparison of submitted data (summary pharmacology studies) and of the abstract shows that important differences exist (e.g. number of patients (51 vs 35), results, etc).

Moreover, according to the applicant, clofarabine pharmacokinetics were dose proportional up to 103 mg/m^2/week. Since the recommended dose for the first cycle of treatment is 30 mg/m^2 daily for 5 consecutives days, it was not clear whether clofarabine pharmacokinetics were still dose proportional at this dosage.

Regarding the ongoing study BIOV-111, data from only five paediatric patients in the metabolism substudy were available.

The results show that after the first dose (day 1), 50% of clofarabine was excreted in the urine over the first 24 hours as unchanged drug and then (up to day 7), a progressive elimination over time.
This suggests a limited accumulation of the unchanged drug.
No data from the possible accumulation of the metabolite was available.

Pharmacokinetics have not been studied specifically in the elderly, while it was already known from the initial application in paediatric patients that renal function may have important implications for clofarabine exposure and toxicity (specific obligation pending). Instead the dose of clofarabine for elderly patients with AML was upfront reduced to 30 mg/m2/day and further decreased based on emerging clinical safety data e.g. increased frequency of renal impairment to 20 mg/m2/day for the second and third cycle.

The full PK report from study CLO-151 should be provided by the MAH as it may provide relevant pharmacokinetic data in elderly patients and may provide further information on the effect of renal function on clofarabine pharmacokinetics.

Pharmacodynamics

Clofarabine's antineoplastic activity has been studied in model systems *in vitro* and *in vivo* and results have been described in the previous submission. The anticancer activity of clofarabine is believed to be due to three mechanisms (DNA polymerase α inhibition, ribonucleotide reductase inhibition, and induction of apoptosis) and these are considered to account for its activity in AML, as in ALL.
No additional data on the pharmacodynamic activity of clofarabine were provided in this submission.

Clinical efficacy

The claimed indication concerns the treatment of AML in elderly patients who have one or more of the following: adverse cytogenetics, secondary AML, ≥ 70 years old or significant co-morbidities and are therefore not considered suitable for intensive chemotherapy. Safety and efficacy have been assessed in studies including patients ≥ 65 years old.

To support this new indication, the MAH submitted a pivotal study BIOV-121 and a key supportive study UWCM-0001.

In the previous submission, a Phase I study established that the recommended daily dose for adults with haematological malignancies was 40 mg/m^2/day, administered by intravenous infusion over 1 hour for 5 consecutive days.
It was further decided to reduce the dose by 25% (30 mg/m^2/day) for the first cycle. The rationale for reducing the dose by 25% was based on possible but non-justified greater toxicity in elderly patients. Due to renal toxicity, 20 mg/m^2/day were administered for the subsequent cycles.

The pivotal study BIOV-121 was an open-label single arm study in elderly patients with AML for whom intensive chemotherapy was not considered suitable. The primary objective was the overall response rate (OR). The OR as the sum of CR, CRi or PR as primary objective is considered relevant since OS and duration of remission (secondary objectives) will allow estimating the clinical benefit of clofarabine.

The OR rate (based on Investigators'assessments) was 48% (95% CI 36-61%) for the FAS and 55% for the PPS. The median duration of response (for patients who achieved CR or CRi) was 63 days (95% CI 43-168 days).
The median OS was 153 days (95% CI 90-255 days). This was better for those patients who achieved a CR or CRi (median 313 days) compared to all treated patients (193 days). Unfortunately, scheduled monthly follow-up including blood counts and follow-up bone marrow examination often did not occur in pivotal study BIOV-121 and study UWCM-0001. The data on duration of remission should thus be interpreted with caution and further information is required. Moreover, separate data for the patient cohorts who achieved CR or CRi should be provided, in order to establish how achievement of CR versus CRi translates into duration of remission/overall survival. A number of patients may have died with relapse AML and were not in remission. As the remission data from these two non-randomised studies provide the major basis for MA, this is a concern.

Even if the results may suggest a possible clinical benefit, they should be interpreted with caution, given the non-comparative design of the pivotal study.
It should be noted that only 39 patients (59%) were assessed by an Independent Response Review Panel (IRRP) with 72% agreement between the Investigator and IRRP assessments.

Moreover, the population included seems too heterogeneous regarding unsuitability for intensive chemotherapy. These criteria (according to the Draft guidelines from the British Committee on Standards in Haematology) were not well defined and some patients, for instance without adverse cytogenetics, were included.
The apparently promising results may be due to a bias of selection of some patients suitable for intensive chemotherapy or of patients with a relatively good prognosis.
As a consequence, an analysis restricted to patients described in the indication and not suitable for intensive treatment should be provided.

The applicant have performed some analyses (e.g., secondary and subgroup efficacy analyses), which were not planned in the original SAP. This SAP was amended after a preliminary review of the data. Therefore, these analyses are only exploratory and cannot be considered even as supportive data.

Moreover, the presentation of results of subgroup analyses is generally confusing.
For example, as stated in the clinical study report, "clofarabine demonstrated a CR rate of 47% (9/19 patients) with a median OS of 227 days in patients with adverse cytogenetics"; knowing that the CR rate in all population (66 patients) was 48 %.

The supportive UWCM-0001 was an open label non-comparative study, which used the same primary objective described for the pivotal study.
Unsuitability for intensive chemotherapy was defined in this study as age ≥ 70 years or age 60-69 years with an ECOG performance score of >2 or history of cardiac disease.
In line with the pivotal study, this population also seems unsuitable for intensive treatment.
It should be noted that 93% of patients in the 30 mg/m^2 cohort had *de novo* AML and only 24% had adverse cytogenetics. This study may have also included patients with a relatively good prognosis.

A limited number of patients (40) were treated in this supportive study. Twenty-nine were treated in the subgroup of interest for this application: the 30 mg/m^2 cohort.
The OR rate was 55%. The median OS was 91 days.
Once more, results of this non-comparative study should be interpreted with caution.

To support the application, comparisons were made between pooled data from the pivotal and the key supportive studies (patients receiving clofarabine 30 mg/m^2/day) and historical comparative data from AML-14 non-intensive study.

The remission rate for clofarabine 30 mg/m^2 (47%) seems significantly higher than that observed with LDAC (20%) and Hydroxyurea (0%).
The median OS was 126 days (95% CI 89-192 days) in the clofarabine group versus 105 days (95% CI 56-165 days). Of note, confidence intervals largely overlap making the difference possibly nil or even against clofarabine.
With reference to one-year survival, no significant difference was observed between the clofarabine (26%) and LDAC (23%) groups.

It must be noted, however, that clofarabine patients were generally younger than those in the AML-14 non-intensive group.
The results may be due to a bias of selection of some patients suitable for intensive chemotherapy in the clofarabine group. Moreover, the comparability between the clofarabine studies and the historical comparative data is questionable (e.g., regarding number and localisation of centres and recording of results).

In the absence of randomisation, no conclusion can be made regarding a potential benefit related to treatment with clofarabine.

Clinical safety

Overall, 155 elderly patients (≥60 years) were treated with clofarabine monotherapy for acute leukaemia or MDS, and 76 elderly patients (≥60 years) were treated with clofarabine in combination with low or intermediate doses of cytarabine for the same conditions.

All patients received clofarabine on a daily x 5 regimen and the majority of patients (173, 75.0%) received a dose of 30 mg/m^2 daily, in the first cycle (including those who did not complete the 5 days of dosing). Fifteen patients (6.5%) received a lower dose in the first cycle and 43 patients (18.6%) received a higher dose in the first cycle. Fifty-six patients received a second cycle of therapy, 16 of whom (38%) received three cycles and five (9%) received more than three cycles.

In pivotal study BIOV-121, the most common treatment-emergent AEs were nausea (66.7% of patients), diarrhoea (60.6%), vomiting (56.1%), thrombocytopenia (48.5%), rash (45.5%) and constipation (40.9%). The majority of events were grade 1 or grade 2 (73.2%). The most common grade 3, 4 or 5 AEs were thrombocytopenia (48.5%), neutropenia (27.3%), neutropenic sepsis (24.2%), and anaemia (22.7%).

The median time to neutrophil recovery was 24 days after the first cycle. This duration of neutropenia, although according to the applicant in a similar range compared to low dose Ara-C, is not significantly different from what has been reported for more intensive ‘standard’ chemotherapy in elderly patients (using daunorubicin and 7 days treatment with Ara-C): between 17-27 days. Treatment with clofarabine may thus be considered as a regimen that induces significant myelosuppression.

Thirty-four patients (52%) in study BIOV-121 reported renal function AEs. For 17 (25.8%) of these patients, the renal function AEs events were of grade 1 or 2, but 17 (25.8%) patients had grade ≥3. Renal toxicity was reported for 12 (30.0%) patients in supportive study UWCM-0001. In 6 patients this was grade 1 or 2 and in 6 patients (15.0%) the worst intensity was grade ≥3. It is of concern that the incidence of renal function AEs in study BIOV-121 and renal toxicity in study UWCM-0001

appeared to be higher and more severe than what was reported in the paediatric ALL studies (see current approved SPC) as well as for other leukaemia treatments in elderly patients. In this context it is relevant that in study BIOV-121 patients had to have adequate renal function to be included (serum creatinine < 1.7 g/dL [or 1.5 x ULN]. Elderly patients may be more at risk of renal insufficiency and concurrent medication may have contributed. The cause of deterioration of renal function needs to be further addressed by the MAH.

Another concern was the liver toxicity reported in the pivotal BIOV-121 study with AST and ALT increases of 32% and 23%, respectively. In study UWCM-0001 raised bilirubin levels were found in 35.0% of patients and raised ALT in 32.5%. In the MDACC randomised study using combination treatment with cytarabine hyperbilirubinaemia was observed in 75.0% of patients and an increased ALT in 69.7%, although the majority were of grade ≤2 (80.7% and 79.2%, respectively). Although according to the MAH, hepatic adverse events were less commonly reported in the investigator sponsored studies CLO-221, DM93-036 and ID00-038, in study CLO-221 three patients (8%) discontinued the study due to drug-related AEs (grade 4 increased ALT).

No conclusion on the post-marketing experience was included in the dossier and the applicant should provide the conclusion of the PSURs in particular with respect to non-expected events.

IV BENEFIT RISK ASSESSMENT

Benefits

The claimed indication concerns the treatment of AML in elderly patients who have one or more of the following: adverse cytogenetics, secondary AML, ≥ 70 years old or significant co-morbidities and are therefore not considered suitable for intensive chemotherapy. Safety and efficacy have been assessed in studies including patients ≥ 65 years old.

In these patients, the currently available options are of limited efficacy. LDAC and HU can be considered palliative treatments and a comparative study (AML-14) suggested that the benefit obtained with LDAC is limited to transient responses without any significant clinical benefit in terms of survival. HU appears even less efficient.
In this context, a treatment that would allow obtaining not only a response but an increase in survival without unbearable toxicity would be welcome.

To support the new indication, the MAH has submitted a pivotal study BIOV-121 and a key supportive study UWCM-0001.

Efficacy data suggest a possible clinical benefit in this severe setting where there is an obvious medical need. In patients not amenable for intensive treatment, supportive options (LDAC or hydroxyurea) do not offer major prolongation in survival.
The claimed indication includes some characteristics that clearly define this high need situation and is in accordance with recent guidelines.

However, three major problems make it difficult to establish a clinical benefit based on the provided studies:

- The pivotal study included a heterogeneous population (without adequate criteria for “unsuitability”) and a non-negligible part of subjects could have received intensive treatment. It cannot be excluded that the favourable outcome observed is at least in part explained by this by-excess recruitment.
- Submitted data are non-controlled (e.g., pivotal study) or controlled but not applicable to the claimed indication. Comparison with published reports using supportive care is poorly demonstrative since populations included in the clofarabine trials and in the published studies might be different. All baseline prognosis-related characteristics in these studies must be described and used for a more detailed analysis before further discussion. Given the difficulty

to perform this analysis, a prospective randomised study with clofararabine versus the best supportive care, LDAC (which is addressed in the ongoing AML 16 trial) should be provided.
- Moreover, the use of combination of true CR rate and CR with incomplete recovery of blood counts (CRi) as surrogate marker for the target population is not adequately justified. No separate data were provided for the group of patients with either CR or CRi with respect to duration of remission/overall survival. These data should be provided, in order to see how achievement of CRi translates into duration of remission/overall survival.

For the time being, the benefit is not established.

Risks

The safety data were collected mainly from the conventional industry-sponsored studies BIOV-121, CLO-221 and ID00-038. Unfortunately, supportive studies UWCM-0001, DM93-036, ID00-038 and the MDACC randomised studies were insufficiently monitored investigator-led studies with different conventions for safety data collection and presentation.
Treatment with clofarabine may be considered as a regimen that induces significant myelosuppression. The median time to neutrophil recovery was 24 days after the first cycle. The most common grade 3, 4 or 5 AEs were thrombocytopenia (48.5%), neutropenia (27.3%), neutropenic sepsis (24.2%), and anaemia (22.7%). It is of concern that the incidence of renal function AEs in study BIOV-121 (25.8% grade ≥3) and renal toxicity in study UWCM-0001 appeared to be higher and more severe than what was reported in the paediatric ALL studies (see current approved SPC) as well as for other leukaemia treatments in elderly patients. In this context it is relevant that in study BIOV-121 patients had to have adequate renal function to be included (serum creatinine < 1.7 g/dL [or 1.5 x ULN]. Elderly patients may be more at risk of renal insufficiency and concurrent medication may have contributed. The cause of deterioration of renal function needs to be further discussed.
The liver toxicity reported in the BIOV-121 study is another concern with AST and ALT increases of 32% and 23%, respectively. In study UWCM-0001 raised bilirubin levels were found in 35.0% of patients and raised ALT in 32.5%.

For the time being, it cannot be concluded that clofarabine is not detrimental to an unacceptable extent in elderly patients.

Balance

For the time being, due to the lack of controlled studies and the lack of outstanding efficacy results, the clinical benefit of clorafabine is not established.
The product appears active (as shown by responses) but the benefit compared to LDAC has not been demonstrated and, if real, could be too limited to compensate for the toxicity observed.

Conclusions

The overall Benefit/Risk balance of Evoltra (clofarabine) in AML elderly patients is for the time being negative.