Annex

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

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Folotyn solution for infusion 20 mg/ml contains pralatrexate, an antineoplastic folate analogue. The proposed indication for pralatrexate is for the treatment of adult patients with peripheral T-cell lymphoma (PTCL) (nodal, other extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy.

- Quality Aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues.

- Nonclinical Aspects

The non-clinical data submitted are considered adequate to support the marketing authorisation application. There are no outstanding non-clinical issues.

- Clinical Aspects

The main efficacy results are derived from the pivotal PDX-008 study (n=109 evaluable patients), with some support from the preceding phase I/II dose-finding PDX-02-078 study (n=15 evaluable patients).

The response rate (defined as the number of responders [complete response (CR) + complete response unconfirmed (Cru) + partial response (PR)] divided by the number of evaluable patients) in PDX-008 study was 29%. Only 15% of patients in the efficacy set obtained confirmed response duration of ≥14 weeks. Response to pralatrexate was of relatively rapid onset, with 63% of responders observed to respond within 1 cycle of treatment as assessed by central review. Responses were noted also in patients resistant to any previous therapy and in patients previously treated with methotrexate. Median Progression-Free Survival (PFS) was 106 days (95% CI, 51-146) according to central review, while 121 days (95% CI, 77-148) based on response assessed by investigator (43/109, 39%). Overall Survival (OS) was 14.5 months (95% CI, 10.6-22.5) with a range of 1.0-24.1 months. Median duration of response (confirmed and unconfirmed) was 306 days (95% CI, 103-not estimable) or 10.1 months, with a range of 1-673 days. Forty-four percent of the responding (confirmed and unconfirmed) patients had a duration of response in excess of 6 months. Not predefined analyses are presented that indicate that pralatrexate induces longer PFS and, in certain analyses, higher response rate than the corresponding estimates, including Time to Progression (TTP), seen in previous lymphoma treatment/s. These analyses are, however, associated with the weaknesses of retrospective analyses and strong assumptions which cannot be tested.

The choice of study design (single arm) as well as primary endpoint (response rate) severely hampers the interpretation of the significance of the results obtained in the PDX-008 study. It has to be pointed out, that CHMP, for this reason, in the protocol assistance given clearly stated that in general, in this setting, neither the design nor the primary endpoint was considered adequate to establish the clinical benefit of a new medicinal product.

The main problem relates to the interpretation of the clinical benefit of the primary endpoint, response. It is actually not known whether or to what extent a response in this setting of PTCL translates into clinical benefit. Tumour response is not a clinical benefit endpoint *per se* and cannot be considered as an established surrogate endpoint for important clinical benefit endpoints such as

PFS and OS. Furthermore, PFS and OS are difficult to interpret in the single-arm design of the pivotal study (and in the absence of dramatic activity).

A related problem is the interpretation of the study results in terms of magnitude. In the absence of generally accepted treatment recommendations and published reports of randomised studies in the setting of relapsed/refractory PTCL, there is no reference point to rely upon in the judgement of response. Results in previously published single-arm studies with other agents are also of very limited value, due mainly to small study populations with often non-comparable entities of T/NK-cell lymphoma. Similarly, registry data are for obvious reasons of limited help and cannot be used for direct comparisons. The presented historical control comparison is not acceptable as evidence of relevant efficacy. Therefore, without a comparator arm, the magnitude of response achieved with pralatrexate in the PDX-008 study cannot be critically assessed. Hence, the clinical efficacy of this agent cannot be considered established in the proposed indication.

The present safety data base, including the experience from performed studies as well as the postmarketing setting, is sufficient to allow characterising the toxicity profile. The overall frequency of pralatrexate-related AEs was high. Most reported side effects were class-specific, expected, and manageable. A high prevalence of mucositis was noted. Deaths related to treatment with pralatrexate were reported. Treatment with pralatrexate is associated with a risk of serious and fatal dermatological reactions that currently cannot be fully predicted or avoided.

In conclusion, the benefits have not been established. In the absence of established benefits, a positive benefit-risk balance cannot be considered established.

Following the CHMP scientific conclusions adopted on 19 January 2012 that Folotyn was not approvable for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy, as in the absence of established benefits a positive benefit-risk balance could not be considered established, the Applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination

Following a request from the Applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group for Oncology inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the Applicant's response.

The Applicant presented in writing and at an oral explanation the grounds that the adopted CHMP Opinion may not have considered the data fully in the proper clinical context for the purpose of assessing the clinical benefits of pralatrexate in an orphan disease setting where there is hitherto no authorised treatment available. Further analyses were provided by the Applicant to support the clinical efficacy of pralatrexate in the proposed indication.

The Applicant outlined the following detailed grounds to be taken into account during the re-examination.

Ground 1 – The magnitude of clinical efficacy of pralatrexate in the treatment of patients with PTCL who have progressed after at least one prior therapy (relapsed/refractory PTCL) can be assessed based on the data provided. These data provide sufficient evidence to support the clinical efficacy of pralatrexate on the following basis:

- Features of the unique mechanism of action of pralatrexate have demonstrated preferential activity in T-cell lymphomas.

- Clinical efficacy in relapsed/refractory PTCL has been demonstrated in both the pivotal study, PDX-008 and the supportive Phase 1/2 study PDX-02-078.
- The clinical efficacy of pralatrexate is demonstrated in PDX-008 through the response rate (29% and 39% by central review and investigator, respectively, with a median duration of response of 12.6 months and a median duration of CR/CRu of 44.2 months), durable responses (59% and 47% of responders with > 6 and > 12 months of response duration, respectively), and clinical benefits achieved through those responses, including the improved outcomes for patients in comparison to their most immediate prior therapy, using patients as their own controls.
- The magnitude of the clinical efficacy benefit of pralatrexate is further confirmed by comparisons to historical database and matched-control analyses, in which pralatrexate demonstrated an improved overall survival (OS) outcome (hazard ratio of 0.39 [95% CI: 0.26, 0.60] and median OS of 19.0 months for pralatrexate vs. 5.8 months for matched controls). Given that the natural course of the disease is well-known and characterised, this approach should be considered appropriate to inform the assessment of clinical efficacy.

Ground 2 – PTCL is an orphan disease with a very aggressive clinical course, and there are no therapies in the EU approved specifically for this indication; thus, pralatrexate addresses a significant unmet medical need.

Ground 3 – Immediate patient access on the public health grounds outweighs the risk inherent in scientific uncertainties surrounding the benefit assessment.

According to the Applicant, the approach taken to conclude a positive benefit-risk balance for pralatrexate is consistent with the established principles set out in the applicable CHMP guidelines, especially the "Guideline on the Evaluation of Anticancer Medicinal Products in Man", and the "Guideline on Clinical Trials in Small Populations."

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant and considered the views of the Scientific Advisory Group.

Regarding Ground 1, the CHMP maintained the view that without a comparator arm, the magnitude of response cannot be critically assessed. The observed activity in terms of response rate cannot be considered dramatic and it is not known whether or to what extent a response might translate into clinical benefit for this patient group.

The Applicant presented an analysis where pralatrexate appears to reverse the trend of decreasing response to successive lines of chemotherapy and decreasing median PFS. However, this type of comparison cannot be considered as convincing to establish efficacy as it relies on strong assumptions, similar to a historical comparison.

The Applicant has provided a matched historical controlled analysis, with comparisons made against OS data. The criteria specified represent key prognostic factors, but there are multiple other potential differences between a clinical trial population, who must satisfy a range of inclusion / exclusion criteria, and those historical databases which will include a broader set of patients. Inclusion criteria for a clinical trial might include a certain life expectancy and performance status; exclusion criteria might include presence of other active concurrent malignancies, cardiac problems

or uncontrolled hypertension, concurrent HIV etc. Any bias introduced by these underlying differences would not be addressed in the primary analysis or either sensitivity analysis.

The Applicant has used medical review to determine the comparability of the matched groupings but the potential for bias remains, as important dissimilarity of treatment and control groups cannot be excluded. For example, it is not possible to determine whether the subjects were treated in a similar setting and manner (potential differences in compliance, concomitant and supportive treatments, adequacy of dose and treatment duration, stage or severity of disease) and thus whether the matches were comparable except for the interventions under consideration.

Overall, externally controlled trials tend to overestimate the effect of test therapies and, despite the magnitude of the effect described, the interpretation that pralatrexate improved OS in comparison to matched historical controls can be considered as hypothesis generating only because of the multiple potential biases which cannot be excluded convincingly.

With respect to Ground 2, the CHMP acknowledged that PTCL is an orphan disease with an aggressive clinical course and a poor prognosis. There are currently no approved therapies in the EU specifically for the claimed indication and there is an unmet medical need. Therefore, the committee agreed that there is a need for new therapies with established efficacy in this disease. However, the submitted clinical data for Folotyn are not considered to be sufficient to inform a favourable benefit-risk assessment. Even if there is currently no consensus on standard therapy for PTCL, the data submitted do not allow drawing any conclusion on the efficacy of Folotyn. Therefore, concerning the arguments presented by the Applicant for Ground 3 the CHMP considered that because the benefits have not been demonstrated the need for immediate access is not justified.

In conclusion, following assessment of the analyses provided in response to the grounds for refusal, the submitted data are still considered insufficient to establish the efficacy of Folotyn in patients with peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated) who have progressed after at least one prior therapy. Therefore, the CHMP has maintained its previous position that the efficacy has not been established.

Grounds for refusal

Whereas

- In the absence of established benefits, a positive benefit-risk balance cannot be considered established.

the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the conditional marketing authorisation for Folotyn.