Annex IV

Scientific conclusions

Scientific conclusions

On 10 March 2016, the European Commission was informed that an increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups had been observed in three clinical trials by the independent safety data monitoring group. The trials evaluated treatment combinations with chemotherapy and immunotherapy which are currently not authorised for Zydelig (idelalisib) in populations with earlier disease characteristics than the currently approved indication. However, in light of the emerging safety data, the European Commission (EC) considered that the findings from the clinical trials and all available safety data related to idelalisib should be reviewed in order to assess their potential impact on the benefit-risk balance of Zydelig in the approved indications and relevant ongoing variations.

On 11 March 2016, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Zydelig (idelalisib) should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

Zydelig (idelalisib) is a centrally authorised product and is currently indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or *TP53* mutation in patients unsuitable for chemo-immunotherapy. Idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment. The CHMP recently adopted a positive opinion to also authorise the use of idelalisib in CLL in combination with another anti CD20 monoclonal antibody, ofatumumab.

This review was initiated due to a reported increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups observed in three clinical trials (GS-US-312-0123, GS-US-313-0124, GS-US-313-0125[1]). The PRAC considered the new interim safety data and very limited efficacy data from three studies (-0123, -0124, -0125), that have been terminated, evaluating the addition of idelalisib to standard therapies in first line CLL and relapsed indolent non-Hodgkin lymphoma (iNHL)/small lymphocytic lymphoma (SLL) as well as the results of all other relevant trials including those that supported the above listed indications. The PRAC noted that in study -0123, idelalisib was administered in combination with rituximab and bendamustine (an unauthorised combination) in previously untreated CLL patients with and without 17p deletion/*TP53* mutation, which is not the same population as the one in the current CLL indication in first line. Similarly, in studies -0124 and -0125 idelalisib was not used as monotherapy as currently authorised but in combination with rituximab or rituximab and bendamustine, respectively. Further, these two studies included patients with earlier disease characteristics than the population for which idelalisib is authorised.

Idelalisib is known to cause very commonly infections and neutropenia and these risks are reflected in the product information. While these risks were considered acceptable due to the demonstrated beneficial effect observed in the studies that supported the initial marketing authorisation and later extension of indication, these three new studies indicate that in patients with early disease (CLL or

[1] GS-US-312-0123 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated CLL
GS-US-313-0124 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with rituximab for previously treated iNHL
GS-US-313-0125 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously treated iNHL

iNHL) the risks (particularly of serious infection) are not outweighed by benefit. There was however no indication that treatment-naïve CLL patients constitute a population more at risk of developing idelalisib-related adverse events compared to relapsed/refractory patients. These results highlight nonetheless the importance of ensuring that the risk of serious infection is adequately minimised in the authorised indications, in line with the measures employed in studies that demonstrated the positive benefit-risk balance of idelalisib. In particular an increased incidence of PJP, carrying a high risk of morbidity and mortality, was observed in the idelalisib treatment arms compared to controls in all the studies, and appeared to be significantly lower in patients administered PJP prophylaxis. No low-risk population or risk-free period could be identified and the risk may persist after end of therapy, therefore, taking into account current guidelines on PJP prophylaxis and in line with the advice from experts consulted during the review (scientific advisory group [SAG]), the PRAC recommended that PJP prophylaxis should be administered to all patients throughout idelalisib treatment and prolonged afterward for up to 6 months based on clinical judgement. CMV infections were also notably reported in the idelalisib treatment arms, however, in controlled studies where idelalisib was administered in combination with rituximab or ofatumumab and not bendamustine, the reported rate was low. Nonetheless, considering the seriousness of those events, and following the SAG advice, the PRAC recommended that patients with evidence of prior CMV infection should undergo regular clinical and laboratory monitoring and patients with CMV viremia should be carefully monitored. If clinical signs of CMV infection appear, consideration should be given to interrupting idelalisib until the infection has resolved. If the benefits of resuming idelalisib are judged to outweigh the risks of CMV, consideration should be given to administering pre-emptive CMV therapy. While CMV and PJP are important risks, in the studies they accounted for a relatively small proportion of the serious infections observed, therefore the PRAC considered that more general measures to minimise the risk of serious infections as implemented as part of the provisional measures were justified. In particular, PRAC recommended that treatment should not be initiated in patients with evidence of ongoing systemic infection, that patients should be monitored for respiratory signs and symptoms throughout treatment and advised to report new respiratory symptoms promptly. Patients' blood counts should also be monitored during the first 6 months of treatment, adapting the frequency to the absolute neutrophil count (ANC). In case of very low ANC ($<500/mm^3$), treatment should be interrupted and may be resumed, at a lower dose, once this has resolved. These recommendations should be reflected in the product information together with a description of the infectious events and the MAH should conduct a study to assess healthcare practitioners' awareness to these risk minimisation measures.

The results of study -0123 are considered of limited relevance to the benefit-risk balance of idelalisib in the authorised CLL indication, due to the added toxicity of bendamustine. In addition, the data suggest that these results reflect the fact that the known toxicity of the treatment was not outweighed by its benefits due to the good prognosis and therefore low disease-related mortality of previously untreated CLL patients. However as patients with 17p deletion or *TP53* mutation have a poor prognosis, the extrapolation of the positive results observed in relapsed/refractory subjects with 17p deletion or *TP53* mutation that supported the initial granting of the indication in patients unsuitable for chemoimmunotherapy is not questioned. Nevertheless, in view of the limited data available in this subset and considering availability of other options for first line treatment for CLL patients, the PRAC was of the view that as a precaution, idelalisib should only be used in patients with 17p deletion or *TP53* mutation if they are not eligible for any other therapies. The benefit-risk balance of idelalisib in combination with rituximab in treatment naïve and relapsed/refractory CLL is therefore considered to remain positive provided the recommended risk minimisation measures are applied. The wording of the indication in first line CLL should be amended to reflect the above recommendation and it should be specified that this is linked to the limited data available in this setting.

For the same reasons, the relevance of the results of study -0123 is considered limited for the benefit-risk balance of idelalisib in combination with ofatumumab in the same types of CLL

patients. The PRAC concluded that the same risk minimisation measures should be applied. Following the same precautionary principle, in view of the limited data available in treatment naïve patients with 17p deletion or *TP53* mutation it was also considered that idelalisib in combination with ofatumumab should be only be used first-line in CLL patients with 17p deletion or *TP53* mutation who are not eligible for any other therapies.

The unfavourable results of studies -0124 and -0125 reflect the use of the additional treatment related toxicity, which is not the same as that of the authorised use in monotherapy. Characteristics of patients in those studies are compatible with a good prognosis, including slow disease progression, hence leading as in study -0123 to an unmasking of the idelalisib toxicity. Therefore while the relevance of these results are also limited for the authorised use in patients refractory to two prior lines of follicular lymphoma treatment, where idelalisib has been demonstrated to be effective and no other effective treatment options exist, they highlight the importance of minimising the risk of serious infection. The PRAC considered that the benefit-risk balance in this indication remained positive provided the risk minimisation measures are implemented. In addition as no controlled study was conducted in this indication, in view of the importance of the risk of serious infections, the MAH should conduct a post-authorisation safety study to collect additional safety data in those patients.

The PRAC concluded that the benefit-risk balance in the authorised indications remained positive, provided that first line treatment with idelalisib is only used in patients with 17p deletion or *TP53* mutation that are not eligible for any other therapies and that changes are implemented in the product information to minimise the risk of serious infections. The PRAC considered that these measures should be applied for the use of idelalisib in combination with ofatumumab in CLL patients.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zydelig (idelalisib).
- The PRAC reviewed the preliminary data provided by the marketing authorisation holder on the interim results of studies GS-US-312-0123, GS-US-313-0124, GS-US-313-0125 that suggested an increased risk of death and serious infection with idelalisib. The PRAC also reviewed all the other relevant data presented by the MAH and the views expressed by the oncology scientific advisory group.
- The PRAC noted that studies -0123, -0124 and -0125 involved patient groups and treatment combinations different from those of the authorised indications of Zydelig. The PRAC considered the results of these studies of limited relevance for the benefit-risk balance of idelalisib in its authorised indications and ongoing extension of indication in combination with ofatumumab for the treatment of CLL. Nevertheless, as a precaution and in view of the fact that limited data are available in treatment-naïve CLL patients with 17p deletion or *TP53* mutation, the PRAC recommended that idelalisib should only be used in this group of patients if they are not eligible for any other therapies.
- The PRAC noted that most of the serious adverse events reported in studies -0123, -0124 and -0125 were related to infections. The PRAC considered that further minimisation measures of the known risk of infection related to the use of idelalisib were necessary. To this effect, the PRAC recommended that treatment with idelalisib should not be initiated in patients with evidence of systemic infections, that patients should be monitored for respiratory symptoms and that they should be administered *Pneumocystis jirovecii*

pneumonia prophylaxis throughout and after idelalisib treatment. Regular clinical and laboratory monitoring for cytomegalovirus infection is also recommended in patients with evidence of prior infection. In addition, neutrophil count monitoring is recommended. In the event of severe neutropenia, treatment should be interrupted and may be restarted at a lower dose upon resolution.

In view of the above, the PRAC concluded that the benefit-risk balance of Zydelig is favourable subject to changes to the product information, as described above.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Zydelig.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CHMP discussed the statement proposed to be added in section 4.4 of the SmPC that limited efficacy and safety data explain why idelalisib is to be used as a first line treatment only in those patients with the 17p deletion or *TP53* mutation who are not eligible for any other therapies. This text was considered not to be contributory as adequate information on the benefit-risk balance of idelalisib in these patients is already included in other sections of the product information. The CHMP therefore concluded that it is not needed to include this statement in the SmPC.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of Zydelig (idelalisib) remains favourable subject to the amendments to the product information.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Zydelig (idelalisib).