17 March 2016
EMA/PRAC/197574/2016

PRAC List of questions

To be addressed by the marketing authorisation holder

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Active substance: idelalisib

Zydelig EMEA/H/A-20/1439/C/3843/0023

Marketing authorisation holder: Gilead Sciences International Ltd

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Background

An increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups has been observed in three clinical trials by the Independent Safety Data Monitoring group. The trials evaluated combinations with chemotherapy and immunotherapy which are currently not authorised for Zydelig (idelalisib), or authorised combination of Zydelig and immunotherapy but in a population with earlier disease characteristics than the currently approved indication. However, in light of the emerging safety data, 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 ongoing extension of indication for use in combination with ofatumumab in chronic lymphocytic leukaemia (CLL). To this effect, the MAH is requested to address the following questions.

Studies 123 to 125 show that if survival on background therapy is very favourable, improved efficacy in terms of survival of an add-on therapy is not possible to demonstrate and AEs leading to death will dominate.

There was, however, also an apparent increase in discontinuations due to safety in these studies compared with studies conducted in patients with poorer prognosis. This might be an issue of competing risk, but could also indicate that some adverse reactions such as autoimmune reactions occur more frequently in the first-line setting or in patients being off-therapy for long. As this might be of importance for the proper use of idelalisib in clinical practice, this list of questions therefore includes the aim to disentangle these two aspects.

2. Questions

Question 1. The MAH is requested to report key safety data overall, including serious adverse events, deaths, discontinuations and reason for discontinuation, as well as for defined treatment durations (by first month, first 3 months, 3- 6 months, >6 months). This should be presented in a tabulated format for the following studies (and any other relevant studies); and the most recent data should be provided:

- GS-US-312-0123
- GS-US-313-0124
- GS-US-313-0125
- GS-US-312-0116
- GS-US-312-0119
- GS-US-313 101-09
- GS-US-313-101-08

For the same studies number of deaths and infectious SAEs should be presented broken down by treatment line in a tabulated format.

Question 2. Based on this presentation, the MAH should compare the results of studies undertaken in the respective diseases for which idelalisib is indicated (CLL including those 17p deletion/TP53 mutations, and follicular lymphoma (FL)), taking different lines of therapy as well as concomitant treatments into account. Based on that, please discuss which characteristics /risk factors that may predict the different results in the studies supporting the currently approved indications and those

raising the safety signal. Furthermore, combination treatment with bendamustine or ofatumumab as risk factor itself for death and infectious SAEs should be evaluated and discussed.

Potential differences in risk minimisation measures implemented within these studies, impact of concomitant medications and line of therapy, the prognostic value of time off therapy prior to initiation of idelalisib therapy as well as mechanistic aspects should be addressed.

Question 3. The MAH should provide a discussion regarding the potential mechanism for the serious adverse events including potential increased risk for autoimmune disorders and infections.

Question 4. The MAH is asked to discuss differences between CLL, and iNHL of putative relevance for safety in general and autoimmune reactions and infections in particular.

Question 5. Provide details as to how many patients received *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in study 116 (and any other relevant study) and how many pts died with/ without prophylaxis, due to PJP, in each study.

Question 6. Regarding the cases of cytomegalovirus infection occurring in these studies, please describe the location of infection, as well as time points when they occurred after treatment initiation.

Question 7. Please provide an updated assessment of the benefit/risk balance in each of the licensed indications as authorised prior to the implementation of the provisional measures recommended at the March PRAC meeting (i.e. in combination with rituximab for the treatment of adult patients with 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, and as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment) and for the new indication for use in combination for ofatumumab in CLL, for which the CHMP has adopted a positive Opinion at its February 2016 meeting.

Question 8. Based on the above evaluation, please provide updated risk minimisation measures recommendations (including changes to the SmPC/PL, proposals to update the RMP and overview of proposed studies), and how their effectiveness should be monitored.