Zydelig

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IA/0053	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	15/09/2021	29/09/2021	SmPC	
IG/1387	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	18/05/2021	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/04/2021	29/09/2021	PL	
IB/0050	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/12/2020	n/a		
IB/0049	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/10/2020	29/09/2021	SmPC and PL	
IA/0048/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	17/03/2020	n/a		
II/0047	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/11/2019	28/02/2020	SmPC, Annex II and PL	The Overall Response Rates (ORRs) reported in the final results of study 101-09 are consistent with the numbers previously reported for both Follicular Lymphoma (FL) patients and the whole study population, with a point estimate approximately 1% higher. The Complete Responses (CRs) in the FL subset doubled, from 8.3 to 16.7%, and the median Duration of Response (DOR) was 12.5 months in all patients and 11.8 in FL patients. The

					Kaplan-Meier estimate of median Overall Survival (OS), including long-term follow-up, was 48.6 months in the overall population, while in FL patients it was 61.2 months. Moreover, the safety findings were consistent with the known safety profile of idelalisib. For more information, please refer to the Summary of Product Characteristics.
II/0046	Submission of the clinical study report for study GS-EU-313-4226, A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig in the European Union; this is a category 3 PASS study to assess the effectiveness of additional risk minimization measures by determining the level of knowledge of haematologists and oncologists (who manage patients with CLL or FL) about the infection risks associated with Zydelig treatment and the corresponding recommendation to minimize these risks as outlined in the SmPC and communicated in the direct healthcare professional communication (DHPC). This is to fulfill RMP post-authorisation measure MEA 016. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/05/2019	n/a		
R/0043	Renewal of the marketing authorisation.	28/02/2019	30/04/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Zydelig in the approved indication remains favourable, but recommended that one additional five-year renewal be

					required based on the following pharmacovigilance grounds: There are still three ongoing studies which are key to the benefit-risk balance as conditions of the marketing authorisation to evaluate the long term safety in patients with relapsed CLL, indolent NHL refractory to rituximab and alkylating agents and haematological malignancies, respectively.
II/0045	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/03/2019	28/02/2020	Annex II	
II/0044	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/03/2019	28/02/2020	Annex II	
PSUSA/10303 /201807	Periodic Safety Update EU Single assessment - idelalisib	14/02/2019	n/a		PRAC Recommendation - maintenance
IA/0041	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	07/08/2018	n/a		
T/0040	Transfer of Marketing Authorisation	25/04/2018	07/06/2018	SmPC, Labelling and PL	
PSUSA/10303 /201707	Periodic Safety Update EU Single assessment - idelalisib	22/02/2018	23/04/2018	SmPC and PL	Please refer to Zydelig PSUSA/00010303/201707 EPAR: Scientific conclusions and grounds recommending the

					variation to the terms of the marketing authorisation
IB/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/03/2018	n/a		
II/0038	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to reflect information from a recent cumulative safety review of cases of organising pneumonia. The safety review resulted from the Marketing authorisation holder (MAH) MAH ongoing pharmacovigilance and signal detection for Zydelig. The RMP version 2.6 has also been submitted to extend the deadlines for submission of final CSRs for three studies linked with Annex II conditions. The MAH took this opportunity to make a minor amendment in the Labelling and to update the local representatives in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	05/03/2018	SmPC, Annex II, Labelling and PL	In the event that moderate or severe symptomatic pneumonitis or organising pneumonia occurs during treatment with Zydelig, it is advised that the treatment with Zydelig should be permanently discontinued. This information is clearly mentioned in section 4.2, 4.4 and 4.8 of the SmPC.
II/0032/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/02/2018		SmPC and PL	

II/0035/G	This was an application for a group of variations. Update of section 5.3 of the SmPC in order to revise the carcinogenicity information for idelalisib based on final results from two long term carcinogenicity studies (TX-312-2017, TX-312-2019). The RMP version 2.3 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2017	05/03/2018	SmPC and Labelling	The carcinogenicity potential of idelalisib was evaluated in a 26 week transgenic RasH2 mouse study and a 2 year rat study. Idelalisib was not carcinogenic at exposures up to 1.4/7.9 fold (male/female) in mice compared to the exposure in patients with haematologic malignancies administered the recommended dose of 150 mg twice daily. A dose related increase in pancreatic islet cell tumors was observed at low incidence in male rats at exposures up to 0.4 fold compared to the human exposure at the recommended dose; a similar finding was not observed in female rats at 0.62 fold exposure margin. This information is reflected in section 5.3 of the SmPC.
PSUSA/10303 /201701	Periodic Safety Update EU Single assessment - idelalisib	14/09/2017	16/11/2017	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10303/201701.
IB/0036	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	31/07/2017	16/11/2017	SmPC	
IB/0033	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	12/05/2017	n/a		
PSUSA/10303 /201607	Periodic Safety Update EU Single assessment - idelalisib	09/02/2017	n/a		PRAC Recommendation - maintenance

IB/0031	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/01/2017	16/11/2017	Annex II	
II/0029	Submission of the final study report for the clinical study 101-07 "A Phase I Study to Investigate the Safety and Clinical Activity of Idelalisib in Combination with Chemotherapeutic Agents, Immunomodulatory Agents and Anti-CD-20 mAb in Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma, Mantle Celle Lymphoma or Chronic Lymphocytic Leukemia", in order to fulfil of the Post Approval Measure (PAM) MEA 009 for Zydelig. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/12/2016	n/a		
IB/0030	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	16/11/2016	16/11/2017	SmPC	
II/0025	Update of section 5.1 of the SmPC to reflect the results of the final report for a study of mechanisms of resistance to idelalisib in patients with chronic lymphocytic leukemia (CLL). This submission fulfils the post-authorisation measure (PAM) 013 for Zydelig.	10/11/2016	16/11/2017	SmPC	In this study, CLL subjects from three Phase 3 clinical trials (GS US 312 0116, GS US 312 0117, and GS US 312 0119) who progressed while on idelalisib treatment were evaluated and a subset was selected for sequencing to identify potential molecular mechanisms of disease progression. Cell sorting identified six (6) subject samples with both high tumour purity and available normal matched

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				tissue. This final analysis showed that there are no coding mutations within this subject set which would reveal a common mutational mechanism of idelalisib resistance, either a mutation in the drug binding site ("gateway mutation") or consistent mutations in any other pathway reflective of a common escape pathway/mechanism. In summary, no mechanistic explanations to the development of resistance to treatment with idelalisib have been identified clinical studies. There are no further ongoing or planned studies in B-cell malignancies aiming to further investigate this topic.
IB/0026	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	07/10/2016	n/a		
IA/0027	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	03/10/2016	n/a		
II/0011	Extension of Indication for Zydelig to include the combination of idelalisib with ofatumumab; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for United Kingdom, Ireland, Slovenia and Slovakia in the Package Leaflet. Furthermore, as a consequence of the art 20 referral procedure (EMEA/H/A-20/1439/C/003843/0023)	25/02/2016	19/09/2016	SmPC and PL	Please refer to the published assessment report Zydelig-H-C-3843-II-0011-AR.

	sections 4.1, 4.4, 4.8 of the SmPC and the package leaflet are updated with a further change introduced in the indication so that idelalisib can be used as first line in patients with 17p deletion or TP53 mutation if they are not eligible for any other therapies. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
A20/0023	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 11 March 2016 the opinion of the European Medicines Agency further to the increased risk of death and serious adverse events observed in three clinical trials among subjects receiving idelalisib. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Zydelig and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.	21/07/2016	15/09/2016		Please refer to the assessment report: Zydelig - EMEA/H/A-20/1439/C/003843/0023
PSUSA/10303 /201601	Periodic Safety Update EU Single assessment - idelalisib	02/09/2016	n/a		PRAC Recommendation - maintenance

II/0018	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding Stevens-Johnson syndrome and toxic epidermal necrolysis based on post marketing experience. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of local representatives in Czech Republic and Slovakia in the Package Leaflet. The updated RMP version 1.9 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2016	15/09/2016	SmPC and PL	Rarely, cases of SJS and TEN have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (bendamustine, rituximab, allopurinol, and amoxicillin). SJS or TEN occurred within one month of the medicinal combination and fatal outcomes have resulted. If SJS or TEN is suspected, idelalisib should be immediately interrupted and the patient treated accordingly.
IAIN/0022/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	31/03/2016	n/a		
PSUSA/10303 /201509	Periodic Safety Update EU Single assessment - idelalisib	17/03/2016	n/a		PRAC Recommendation - maintenance

II/0017	Update of section 4.5 of the SmPC in order to amend the clinical recommendations for the co-administration of idelalisib with anticoagulants. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to amend the contact details of the local representatives for Belgium and Luxemburg in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	15/09/2016	SmPC and PL	A clinically relevant interaction following co-administration of rivaroxaban with idelalisib is not anticipated, and therefore rivaroxaban has been removed from the list of potential interactions for Zydelig.
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2016	n/a		
IB/0019/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2016	11/02/2016	Annex II	
IG/0624	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2016	n/a		
PSUSA/10303 /201503	Periodic Safety Update EU Single assessment - idelalisib	10/09/2015	n/a		PRAC Recommendation - maintenance

IB/0013	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	17/08/2015	n/a		
IG/0599	B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method	12/08/2015	n/a		
IG/0595	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	04/08/2015	n/a		
IG/0583	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		
IB/0010	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	06/07/2015	11/02/2016	SmPC	
II/0008/G	This was an application for a group of variations. Submission of the final study reports of the in vitro and in vivo preclinical studies performed to characterize the immune consequences of idelalisib treatment in fulfilment of the post-authorisation measure MEA 012.	25/06/2015	n/a		N/A

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0006	Update of sections 4.8 and 5.1 of the SmPC, after submission of Final CSR for study GS-US-312-0116, in order to, respectively, update the safety information regarding rash and update the SmPC with final efficacy data. The relevant Annex II obligation was amended to reflect the submission of the final study report for GS-US-312-0116. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct typographical errors concerning repeated dose toxicity studies in rats and dogs in section 5.3 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	11/02/2016	SmPC and Annex II	Final efficacy and safety data from study GS-US-312-0116 have been included in the product information for Zydelig. The data are consistent with the data presented in the first and second interim analyses submitted in the course of the Marketing Authorisation Application.
IG/0521	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer	26/02/2015	11/02/2016	Annex II and PL	

	responsible for batch release				
II/0005	Submission of the final study report for the non-clinical study AD-312-2029, in vitro assessment of idelalisib as a substrate for human OATP1B1 and OATP1B3 over an extended concentration range, in fulfilment of the Post Approval Measure (PAM) 004 for Zydelig; this PAM was agreed during the assessment of the marketing authorisation application for Zydelig. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
II/0004	Submission of the final study report for the non-clinical study AD-312-2030, a study on the human enzymology of idelalisib oxidation, in fulfilment of the Post Approval Measure (PAM) 003 for Zydelig; this PAM was agreed during the assessment of the marketing authorisation application for Zydelig. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
IB/0003/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/12/2014	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
II/0002	Submission of the final non-clinical study report for Study PC-312-2016; a radioligand binding assay with GS-563117. No changes to the product information are proposed. The provision of the study report addresses MEA 011. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2014	n/a		As agreed with the CHMP during the initial MA procedure, the MAH has submitted data from a receptor screen with the main human metabolite GS-563117. No activity of importance was seen among 87 targets. In combination with the mouse toxicity study submitted in the parallel variation procedure II-01, these data support the view that GS-563117 is unlikely to contribute significantly to the toxicity of idelalisib. This post-approval measure (MEA 011) is considered fulfilled. No changes to the product information are necessary as a result of this study. These data do not have any impact on the benefit/risk balance of the product, which remains positive.
II/0001	Submission of the final non-clinical study report for Study TX-312-2018; a 4-Week Oral Dose Range-Finding Toxicity and Toxicokinetic Oral Gavage Study with Idelalisib in 001178-W (Wild Type) RasH2 Mice. No changes to the product information are proposed. The provision of the study report addresses MEA 010. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2014	n/a		As agreed with the CHMP during the initial MA procedure, the MAH has submitted data from a 4-week range-finding study in rasH2 (wildtype) mice. In contrast to what was seen in rats and dogs, exposure to the main human metabolite GS-563117 was substantial. No toxicity which could be attributed to the metabolite was seen, and the company considers the metabolite toxicologically qualified by this study. Formally, this is not fully correct since the AUC did not reach human exposure. However, idelalisib is in itself toxic and exposure margins at the MTD for idelalisib were small. Toxicity appears to be solely related to the pharmacological activity, and the metabolite shows no activity (this is further addressed in the parallel variation

					procedure II-02). In totality, it is concluded that GS-563117 is unlikely to contribute significantly to the toxicity of idelalisib. This post-approval measure (MEA 010) is considered fulfilled. No changes to the product information are necessary as a result of this study. These data have no impact on the benefit/risk balance of the product which remains positive.