Revolade

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
II/0068	Extension of indication to include treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) irrespective of time since initial diagnosis, based on an ad-hoc analysis of Study TAPER (CETB115J2411); an ongoing phase II, open-label, prospective, single-arm study in	15/09/2022	14/10/2022	SmPC	Please refer to Scientific Discussion 'Revolade-H-C-1110/II/0068'

[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).

	adult ITP patients who are refractory or relapsed after first-line steroids. As a consequence sections 4.1 and 5.1 of the SmPC have been updated. In addition, the MAH took the opportunity to make some minor amendments in section 4.8 of the SmPC for increased consistency. An updated RMP version 54.1 has been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
PSUSA/1205/ 202109	Periodic Safety Update EU Single assessment - eltrombopag	05/05/2022	n/a		PRAC Recommendation - maintenance
IB/0066/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change	15/12/2021	04/02/2022	Annex II and PL	

	in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of				

	the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
IAIN/0065/G	This was an application for a group of variations.	01/09/2021	04/02/2022	Annex II and	

	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing 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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation			PL	
IA/0064/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information 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	07/04/2021	n/a		
II/0063	Update of sections 4.2, 4.8 and 5.2 of SmPC to	14/01/2021	04/02/2022	SmPC, Annex	Update of sections 4.2, 4.8 and 5.2 of SmPC to clarify

	clarify dosing recommendations to ensure accurate treatment of patients of 'East-/Southeast-Asian' ancestry and to correct the ADR list based on currently available data, which was previously submitted and reviewed. Update of section 4.4 of the SmPC in line with the 'Excipients in the labelling and package leaflet of medicinal products for human use'. The Package leaflet has been updated accordingly. Editorial changes have also been introduced in the PI. An updated RMP has been submitted to update the final due date i.e. the date for the provision of the primary study report of CETB115E2201 (category 3) in the RMP and removal of important safety concerns, already endorsed by PRAC in the PSUSA procedure (EMEA/H/C/PSUSA/00001205/201809). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			II, Labelling and PL	dosing recommendations for all patients of 'East-/Southeast-Asian' ancestry. For more information, please refer to the Summary of Product Characteristics.
IAIN/0062	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	24/07/2020	14/12/2020	SmPC	
IB/0060/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	02/07/2020	n/a		

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished				

	product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products				
IB/0061	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	20/05/2020	n/a		
IA/0059/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 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	27/03/2020	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IB/0058/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 A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	13/01/2020	14/12/2020	Annex II and PL	

	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0057/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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	19/12/2019	14/12/2020	Annex II and PL	

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change				

	in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging -				

	Device with CE marking B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
PSUSA/1205/ 201809	Periodic Safety Update EU Single assessment - eltrombopag	11/04/2019	n/a		PRAC Recommendation - maintenance
IB/0056/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished	01/04/2019	n/a		

	product - Other changes to a test procedure (including replacement or addition)				
II/0050	Change of the Revolade indication of immune thrombocytopenic purpura to specify the duration of the disease. As a result, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 have been revised. The Package leaflet has been updated accordingly. Furthermore, minor editorial changes have been introduced in the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	13/12/2018	06/02/2019	SmPC and PL	Please refer to the Scientific Discussion document: Revolade H-1110-II-50
II/0046	Update of the SmPC in follow-up to the transfer of the marketing authorisation and as part of routine pharmacovigilance activities/update of the Company's Core Safety Data Sheet in order to update information related to liver function tests, thrombotic and thromboembolic complications and MDS in section 4.4; update DDI and food interaction information in sections 4.5 and 5.2; include and remove ADRs as well as change some ADRs frequencies following pooling of safety data in section 4.8; reorganise information on severe aplastic anaemia in section 5.1; update information related to Juvenile animal studies in section 5.3. The MAH took the opportunity to make some editorial changes throughout the PI. The Package leaflet is updated accordingly.	24/01/2019	18/12/2019	SmPC and PL	No case of thrombotic/thromboembolic (TEE) complications was identified from a clinical study in refractory SAA, however the risk of these events cannot be excluded in this patient population due to the limited number of exposed patients. As the highest authorised dose is indicated for patients with SAA (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population. There is a theoretical concern that TPO-R agonists may stimulate the progression of existing haematological malignancies such as MDS. The co-administration of 200 mg ciclosporin decreased the Cmax and the AUCinf of eltrombopag by 25% and 18%, respectively. The co-administration of 600 mg ciclosporin decreased the Cmax and the AUCinf of eltrombopag by 39% and 24%, respectively. Concomitant administration of eltrombopag with a high-

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				calcium meal may affect exposure to eltrombopag (for more information please refer to the Summary of Product Characteristics). Food low in calcium (<50 mg calcium), including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain, did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5). At non-tolerated doses in pre-weaning rats, ocular opacities were observed. At tolerated doses, no ocular opacities were observed. In conclusion, taking into account the exposure margins based on AUC, a risk of eltrombopag-related cataracts in paediatric patients cannot be excluded. For more information please refer to the Summary of Product Characteristics.
II/0053	Update of sections 4.4 and 4.8 of the SmPC in order to extend the warning on cytogenetic abnormalities to reflect the incidence of new genetic abnormalities following data from study ELT116826 (AUS18T) – An open-label, single center, non-randomized, phase 2, dose modification pilot study of a Thrombopoietin-Receptor Agonist (TPO-R Agonist), eltrombopag, in aplastic anemia patients with immunosuppressive-therapy refractory thrombocytopenia, listed as a category 3 study in the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/01/2019	18/12/2019	SmPC	In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months. In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one

					patient had cytogenetic abnormality at Month 6.
II/0052/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.7 - Administrative change - Deletion of manufacturing sites 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 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 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 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 B.I.a.1.g - Change in the manufacturer of AS or of a	15/11/2018	n/a		

	starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0054	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/10/2018	n/a		

PSUSA/1205/201709	Periodic Safety Update EU Single assessment - eltrombopag	26/04/2018	06/07/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1205/201709.
IAIN/0051/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	31/05/2018	n/a		
T/0047	Transfer of Marketing Authorisation	16/03/2018	06/04/2018	SmPC, Labelling and PL	
IB/0048	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	14/03/2018	n/a		

	authorisation, including the RMP - Other variation				
IB/0045/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.IV.1.z - Change of a measuring or administration device - Other variation	24/02/2018	06/04/2018	SmPC, Annex II, Labelling and PL	
PSUSA/1205/ 201609	Periodic Safety Update EU Single assessment - eltrombopag	18/05/2017	19/07/2017	Annex II	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1205/201609.
IB/0043	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/07/2017	n/a		
II/0042	Submission of the ASPIRE (TRC114968) final study report, a Three-Part Study of eltrombopag in Thrombocytopenic Subjects with Myelodysplastic Syndromes or Acute Myeloid Leukemia (Part 1: Open-Label, Part 2:Randomized, Double-Blind, Part 3: Extension) assessing the potential risk of haematological changes, optimal dose escalation scheme and eltrombopag pharmacokinetics. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/06/2017	n/a		
II/0040	Submission of the final data from the nested eltrombopag HCV-TARGET cohort study in HCV	26/01/2017	n/a		

	associated thrombocytopenia in patients undergoing interferon based anti-HCV treatment with DAAs in fulfilment of MEAs 025.2 and 025.3. An updated RMP version 44.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0039	Submission of final report of the Drug Utilization Study REVIEU (CETB115B2406) assessing eltrombopag utilisation patterns and characterising patients treated with eltrombopag in routine clinical practice in fulfilment of MEA 021.1. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2017	n/a		
II/0037/G	This was an application for a group of variations. Update of SmPC section 4.8 to add a new ADR 'skin discolouration' with the frequency 'not known'. The PL has been updated accordingly. Additionally, minor editorial changes have been introduced throughout the PI. The MAH took also the opportunity to align the PI with the latest version of the QRD template 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	24/11/2016	16/02/2017	SmPC, Labelling and PL	

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0036/G	This was an application for a group of variations. Update to the Annex II of the Product Information based on the study assessing Effectiveness of eltrombopag Educational Materials for Hepatitis C associated thrombocytopenia; update of the RMP (v. 41) to remove the PASS Study PLATELET from the Pharmacovigilance Plan; submission of the ENABLE-TEE final study report, an Observational Follow-up Study of Patients who Experienced Thromboembolic Events in the ENABLE studies. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	13/10/2016	16/02/2017	Annex II	

	of studies to the competent authority				
II/0035/G	This was an application for a group of variations. Submission of the final study report of study TRC112765 assessing safety of eltrombopag in subjects with solid tumours receiving gemcitabine monotherapy or gemcitabine plus cisplatin or carboplatin; the RMP version 42 has been updated accordingly. In addition, the MAH took the opportunity to revise due dates for submission of final reports for two studies in the Pharmacovigilance Plan. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority 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	13/10/2016	n/a		
II/0032	Update of the SmPC sections 4.4 and 4.8 with new information on the drug-induced liver injury. Consequently, the key elements to be included in the educational material section of the Annex II have been updated. The RMP (v. 42) has been revised accordingly.	13/10/2016	16/02/2017	SmPC and Annex II	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0038	A.7 - Administrative change - Deletion of manufacturing sites	07/10/2016	n/a		
IB/0033	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/07/2016	n/a		
IAIN/0034/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a	26/05/2016	16/02/2017	Annex II and PL	

	manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
II/0029/G	This was an application for a group of variations. Update of the section 5.1 of the SmPC with the exposure data from study TRA105325 (EXTEND (Eltrombopag eXTENded Dosing study) an extension study of eltrombopag olamine (SB-497115-GR) in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP) previously enrolled in an eltrombopag study). A minor change was also introduced in section 4.8 of the SmPC. In addition, the MAH took the opportunity to propose an update of the due date in the RMP for the provision of the final CSR for the study assessing effectiveness of Educational Materials for Hepatitis C associated thrombocytopenia. A revised RMP version 38 was approved as part of the application.	26/05/2016	16/02/2017	SmPC	Eltrombopag was administered to 302 ITP patients in the open-label extension study EXTEND (TRA105325), 218 patients completed 1 year, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 years. The median baseline platelet count was 19,000/µl prior to eltrombopag administration. Median platelet counts at 1, 2, 3, 4, 5, 6 and 7 years on study were 85,000/µl, 85,000/ µl, 105,000/µl, 64,000/µl, 75,000/µl, 119,000/µl and 76,000/µl, respectively. Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. Across the clinical development programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In a small number of ITP patients, eltrombopag treatment was discontinued due to bone

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				marrow reticulin.
PSUSA/1205/ 201509	Periodic Safety Update EU Single assessment - eltrombopag	14/04/2016	n/a		PRAC Recommendation - maintenance
X/0022/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/01/2016	04/04/2016	SmPC, Labelling and PL	Please refer to the Scientific Discussion document: Revolade H-1110-X-22G
II/0030	Update of sections 4.5 and 5.2 of the SmPC based on the study report of the drug-drug interaction with cyclosporin (RAD201583). The Package Leaflet is updated accordingly. The updated RMP version 37.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	16/02/2017	SmPC and PL	In this variation the PI has been updated to add information that in vitro studies demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. A decrease in eltrombopag exposure was observed with co-administration of 200 mg and 600 mg ciclosporin (a BCRP inhibitor). Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count. Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on

					these platelet counts.
II/0023	Extension of indication to extend the use of Revolade to non-splenectomized patients; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/12/2015	28/01/2016	SmPC and PL	Please refer to the Scientific Discussion Revolade-H-C-1110-II-23.
II/0024	Update of section 4.8 of the SmPC in order to include gingivitis, skin infection and mouth ulceration as new adverse reactions following a review of undesirable effects in chronic ITP patients conducted at the request of the CHMP subsequent to the renewal procedure. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/01/2016	SmPC and PL	
II/0020	Extension of Indication to include the treatment of adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The package leaflet is updated accordingly. In addition, the acronym used for full blood counts (FBC) in the	23/07/2015	25/08/2015	SmPC, Annex II and PL	Please refer to the Scientific Discussion Revolade-H-C-1110-II-20.

	SmPC, Annex II and PL is being corrected. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0027/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	13/07/2015	25/08/2015	Annex II and PL	
II/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/06/2015	n/a		
II/0019	Update of the RMP to include 'thrombotic microangiopathy' as an important potential risk. Further, administrative changes have been introduced in the RMP sections SIV.3 Pregnant or lactating women, SV.2 non-study post-authorisation exposure and Part III Pharmacovigilance Plan. The revised RMP version 32 was agreed as part of the procedure.	25/06/2015	n/a		N/A

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/1205/ 201409	Periodic Safety Update EU Single assessment - eltrombopag	07/05/2015	n/a		PRAC Recommendation - maintenance
T/0025	Transfer of Marketing Authorisation from GlaxoSmithKline Trading Services Limited to Novartis Europharm Limited. Transfer of Marketing Authorisation	07/04/2015	06/05/2015	SmPC, Labelling and PL	
R/0018	Renewal of the marketing authorisation.	20/11/2014	15/01/2015	SmPC, Annex II and PL	Based on the review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and, therefore, considered that the benefit risk of Revolade continues to be favourable. Based on the data reviewed, the CHMP recommended updating Section 4.8 of the SmPC to add musculoskeletal pain, back pain and menorrhagia adverse reactions as common events. The PL was updated accordingly. In addition, amendments to the SmPC, the Annex II, the labelling and the PL were introduced in line with the latest QRD template. The RMP was updated. These changes do not affect the risk-benefit balance of the product, which remains positive. In view of the data submitted by the MAH, the CHMP recommends that the renewal of the Marketing Authorisation be granted with unlimited validity.

II/0014/G	This was an application for a group of variations. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required 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	23/10/2014	n/a		
IG/0442	A.1 - Administrative change - Change in the name and/or address of the MAH	05/06/2014	15/01/2015	SmPC, Labelling and PL	
II/0015/G	This was an application for a group of variations. The MAH proposed to amend section 4.5 of the SmPC in order to update the wording related to HCV protease inhibitors, based on the results of a drug-drug pharmacokinetics (PK) interaction study of boceprevir or telaprevir with eltrombopag, and the	22/05/2014	15/01/2015	SmPC and PL	The MAH submitted the final CSR for the study TPL116010 to address some of the limitations concerning the lack of data of co-administration of eltrombopag in combination with direct acting antivirals (DAAs) (i.e. boceprevir/telaprevir. No relevant interaction between telaprevir-eltrombopag was shown and thus no dose adjustments are necessary. With respect to boceprevir, the

	wording on HMG CoA reductase inhibitors based on a literature review. In addition, the MAH has reviewed the information of the labelling of eltrombpag and have incorporated some changes in the Package Leaflet (PL) in alignment with the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Cmax value was increased by 20% and the Cmin is decreased by 32%. Even though the magnitude of the changes is not substantial in absolute terms, the clinical relevance of the decrease in Cmin has not been established. Nevertheless, in line with recommendations previously made for similar clinical situations, increased clinical and laboratory monitoring for HCV suppression is recommended. In addition, further to a literature review, information regarding HMG-CoA reductase inhibitors has been updated to provide consistent information about the use of all statins when co-administered with eltrombopag. Changes in the PL of eltrombopag have been incorporated in order to align the side effects with the SmPC.
PSUV/0016	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
X/0012/G	This was an application for a group of variations. Extension of the Marketing Authorisation concerning a new strength of 75 mg film-coated tablet. Extension of indication for Revolade in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia. Consequently, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. Moreover, the key elements to be included in the educational material in Annex II and the package leaflet have been updated accordingly. In addition, the product information has been revised in line with QRD template version 9.0 and the list of local representatives in the package leaflet has been	25/07/2013	19/09/2013	SmPC, Annex II, Labelling and PL	Please refer to Assessment Report H-1110-X-12G-AR.

	amended. Variation for Revolade to lower the threshold for drug related impurities. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
IG/0275	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2013	n/a		
II/0010	Update of section 4.4 of the SmPC in order to strengthen a warning relating to the risk of MDS progression following treatment with TPO-R agonists as requested by the CHMP following the assessment of FU2 008.1. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.1. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	In clinical studies with a Thrombopoetin Receptor (TPO-R) agonist in patients with myelodysplastic syndrome (MDS), cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported. Forty-two post-marketing cases of progression with concomitant use of eltrombopag have also been reported. Although a causal relationship of the MDS progression with eltrombopag could not be established, the diagnosis of ITP in adults and elderly patients, candidates for eltrombopag treatment, should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Eltrombopag should not be used for the treatment of thrombocytopenia due to

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				MDS or any other cause of thrombocytopenia other than ITP outside of clinical trials.
IG/0150/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	05/04/2012	n/a		
IA/0008/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	22/09/2011	n/a	Annex II and PL	
II/0005	Changes in sections 4.2, 4.4, 4.8 and 5.2 of the SmPC to update the recommendations for the treatment of patients with hepatic impairment further to the final results from the clinical study TPL 104054 (ELEVATE) and the population PK/PD report	17/02/2011	02/05/2011	SmPC, Annex II, Labelling and PL	The recommendations for the treatment of patients with hepatic impairment have been updated in the SmPC further to the final results from the clinical study TPL 104054 (ELEVATE) and the population PK/PD report RA 018247. The main changes included the extension of the

	RA 018247. Moreover Annex II has been updated accordingly on the conditions or restrictions with regard to the safe and effective use of the medicinal product. In addition the date of first authorisation and marketing authorisation numbers have been included in the SmPC and marketing authorisation numbers have been included in the labelling. Finally, the SmPC, Annex II and PL include minor editing changes and have been updated to the latest version of the QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				recommendation to all patients with hepatic impairment (Child-Pugh score ?5) in section 4.2 and the update of the warnings related to the risk of thromboembolic events in sections 4.4 and 4.8. In addition PK data in patients with hepatic impairment has been updated in section 5.2. Moreover the key elements to be included in the educational materials with regards to the conditions of the Marketing Authorisation in Annex II have been updated accordingly.
IB/0006/G	This was an application for a group of variations. 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 B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	07/03/2011	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0007/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	04/02/2011	n/a		

IG/0034/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	06/01/2011	n/a	Annex II	

IB/0004	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	27/08/2010	n/a		
IB/0003	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	27/08/2010	n/a		
IB/0002	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	27/08/2010	n/a		
IB/0001	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	27/08/2010	n/a		