Rydapt

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/0029	Update of section 4.8 of the SmPC in order to add "Acute febrile neutrophilic dermatosis" to the list of adverse drug reactions (ADRs) with frequency not known based on pre-clinical data, clinical trial datasets, scientific literature and safety databases. The Package Leaflet is updated accordingly. The MAH	22/06/2023		SmPC and PL	

[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).

	took the occasion to also include some editorial/formatting changes in the Product information. The MAH has also taken the occasion to align the annex A to the correct expression of pack size as included in the registered system (Siamed). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0030	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/05/2023	n/a		
II/0028	Update of sections 4.2 and 5.2 of the SmPC in order to update efficacy and safety information in elderly patients based on final results from study CPKC412A2408 - An open-label, multi-center, Phase IIIb study to assess the safety and efficacy of midostaurin (PKC412) in patients 18 years of age or older with newly diagnosed FLT3-mutated Acute Myeloid Leukemia who are eligible for "7+3" or "5+2" chemotherapy, listed as a PAES in the Annex II. The RMP version 8.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/03/2023		SmPC and Annex II	Considering the additional safety data provided in elderly patients through the study CPKC412A2408 which indicate the same level of safety in such older population, the sentence: "There is limited experience with midostaurin in AML patients aged 60 70 years and no experience in AML patients above 70 years" has been deleted from section 4.2 of the SmPC. For more information, please refer to the Summary of Product Characteristics.
IA/0027/G	This was an application for a group of variations.	16/12/2022	n/a		

	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits				
II/0024	C.I.11.b Submission of the final report from study CPKC412E2301 listed as an obligation in the Annex II of the Product Information. This is a Phase III study to investigate the efficacy in elderly patients. A final pharmacogenomic report is also provided to fulfil MEA004. The Annex II and the RMP (submitted version 7.0) are updated accordingly. 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	15/09/2022		Annex II	Not Applicable

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/10638 /202110	Periodic Safety Update EU Single assessment - midostaurin	10/06/2022	n/a		PRAC Recommendation - maintenance
R/0023	Renewal of the marketing authorisation.	24/03/2022	30/05/2022	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Rydapt in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Rydapt (midostaurin) is removed from the additional monitoring list as a new active substance following five years of authorisation. As a result the black triangle and relevant warnings are being removed from PI
II/0018/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4,Update SmPC in section 4.5 in order to add drug-drug interaction information with P-gp, BCRP, CYP2D6, substrates (digoxin, rosuvastatin, and dextromethorphan), based on final results from study CPKC412A2121, a Phase 1, open-label, drug-drug interaction study, listed as category 3 study in the RMP; section 5.2 of the SmPC and the Package Leaflet is updated accordingly. (MEA 005.3)	27/01/2022	04/03/2022	SmPC and PL	SmPC new text Section 4.2 Under Hepatic impairment it is added that "Exposure to midostaurin and its active metabolite CGP62221 is substantially lower in patients with severe hepatic impairment than that in patients with normal hepatic function (see section 5.2). However, there are insufficient efficacy data in patients with severe hepatic impairment to suggest a dose adjustment is required." The relevant warning is removed from section 4.4. Section 4.5 Information in section "Effect of Rydapt on other medicinal products" is updated to reflect new information. Substrates of CYP enzymes and Substrates of transporters

	C.I.4,Update SmPC in section 4.5 in order to add drug-drug interaction information with CYP2B6, CYP2C8, CYP3A4 substrates, based on final results from study CPKC412A2122, a Phase 1, open-label, drug-drug interaction study, listed as category 3 study in the RMP; section 5.2 of the SmPC and the Package Leaflet is updated accordingly. (MEA 007.2) C.I.4 Update SmPC in section 4.5 in order to add drug-drug interaction information with oral contraceptives , and section 4.6 to update information on pregnancy and contraception based on final results from study CPKC412A2123, a Phase 1, open-label, drug-drug interaction study, listed as category 3 study in the RMP; the Package Leaflet is updated accordingly. (MEA 008.2) C.I.4 Update SmPC in section 5.2 in order to update pharmacokinetic information on OATP1B1 transporters based on final results from PBPK modelling study DMPK R2000528 listed as category 3 studies in the RMP (MEA 009); C.I.4 Update SmPC in section 4.2 in order to amend posology instructions, section 4.4 to amend an existing warning and section 5.2 to update pharmacokinetic information for patients with severe hepatic impairement, based on final results from study CPKC412A2116 listed as category 3 study in the RMP. This is an open label, multiple dose study to evaluate the PK of midostaurin in subjects with mild, moderate and severe hepatic impairment				Medicinal products with a narrow therapeutic range that are substrates of CYP2B6 (e.g. bupropion or efavirenz), CYP1A2 (e.g. bupropion or efavirenz), CYP2E1 (e.g. chlorzoxazone), of the transporter BCRP BCRP (e.g. rosuvastatin or atorvastatin) should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure. Hormonal contraceptives (containing ethinyl estradiol and levonorgestrel in healthy women): It is not anticipated that the contraceptive reliability of this combination will be compromised by co-administration of midostaurin. Section 5.1 Updated ATC code: L01EX10 Section 5.2 is updated accordingly For more information, please refer to the Summary of Product Characteristics.

	compared to matched healthy subjects; (MEA010) The RMP version 6.0 has also been submitted. In addition, MAH takes this opportunity to introduce minor changes to edit the wording related to the ethanol excipient in the Package Leaflet, according the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668), by rounding the volume of alcohol to the next integer number, i.e. from 16.9 to 17 ml. The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). 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 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 A.6 - Administrative change - Change in ATC Code/ATC Vet Code				

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0022	Update of section 5.1 of the SmPC in order to update efficacy information in elderly patients, based on final results from study ADE02T listed as PAES in the Annex II; this is a phase II study to investigate the efficacy of midostaurin in combination with intensive induction, consolidation including allogenic SCT and single agent maintenance in patients aged 18-70 with FLT3 ITD mutated AML. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/12/2021	04/03/2022	SmPC and Annex II	Section 5.1: Efficacy and safety results in patients >60 70 years old evaluated as part of a phase II, single arm, investigator initiated study of midostaurin in combination with intensive induction, consolidation including allogenic SCT and single agent maintenance in patients with FLT3 ITD mutated AML are updated to reflect that "Based on the final analysis, the EFS rate at 2 years (primary endpoint) was 34% (95% CI: 27, 44) and the median OS was 22.7 months in patients older than 60 years of age (128 out of 440 patients). For more information, please refer to the Summary of Product Characteristics.
IB/0020/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	19/08/2021	n/a		

	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)				

	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure				
PSUSA/10638 /202010	Periodic Safety Update EU Single assessment - midostaurin	24/06/2021	18/08/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10638/202010.
IA/0021	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	17/08/2021	n/a		
IA/0019/G	This was an application for a group of variations. B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	01/07/2021	n/a		
II/0014	C.I.4 Update of sections 4.2, and 4.4 of the SmPC in order to change posology recommendations and add Special warnings and precautions for use in	10/12/2020	22/01/2021	SmPC, Labelling and PL	• Sections 4.2 the text for Paediatric population is changed to: "Rydapt should not be used in combination with intensive paediatric AML combination chemotherapy regimens

	Paediatric population following the occurrence of severe dose limiting toxicities (DLTs) in the pediatric study CPKC412A2218 which is currently on clinical hold. The study is part of the agreed PIP (EMEA-000780-PIP01-09-M05) for which a Request for Modification was submitted on 20-Apr-2020. Section 5.1 of the SmPC and the Package Leaflet are updated accordingly. The RMP version 5.0 has also been submitted. In addition, the MAH takes this opportunity to introduce minor editorial changes to align the PI to the updated QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				including anthracyclines, fludarabine and cytarabine because of the risk of prolonged haematological recovery (such as prolonged severe neutropenia and thrombocytopenia) (see sections 4.4 and 5.1)". The same is added as warning in section 4.4. • In section 5.1 section of Paediatric population the following is added: "In a phase II study where, midostaurin was investigated in combination with chemotherapy in newly diagnosed paediatric patients with FLT3-mutated AML. Among the three FLT3-mutated AML patients enrolled in the study, two patients (10 and 14 years old) experienced dose limiting toxicities (DLTs) following the second induction cycle with midostaurin (at 30 mg/m2 twice daily) in combination with chemotherapy (containing cytarabine 2 g/m2/day, day 1-5; fludarabine 30 mg/m2/day, day 1-5 and idarubicin 12 mg/m2/day, day 2, 4 and 6). Both patients showed markedly delayed haematological recoveries (i.e. prolonged grade 4 thrombocytopenia lasting for 44 days in the first patient and 51 days in the second patient and grade 4 neutropenia lasting for 46 days in the second patient). In the first induction cycle both patients received midostaurin in combination with cytarabine, etoposide and idarubicin".
IA/0016	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	16/12/2020	n/a		
IA/0015/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	20/08/2020	n/a		

	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 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.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IB/0013	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/06/2020	22/01/2021	Annex II	
PSUSA/10638 /201910	Periodic Safety Update EU Single assessment - midostaurin	14/05/2020	n/a		PRAC Recommendation - maintenance
IB/0011	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/01/2020	n/a		

PSUSA/10638 /201904	Periodic Safety Update EU Single assessment - midostaurin	28/11/2019	n/a		PRAC Recommendation - maintenance
IAIN/0010/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) 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) 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) 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	26/08/2019	n/a		
IB/0008	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	25/07/2019	n/a		
PSUSA/10638 /201810	Periodic Safety Update EU Single assessment - midostaurin	16/05/2019	n/a		PRAC Recommendation - maintenance
IA/0007/G	This was an application for a group of variations.	10/05/2019	n/a		

	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.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure				
PSUSA/10638 /201803	Periodic Safety Update EU Single assessment - midostaurin	04/10/2018	n/a		PRAC Recommendation - maintenance
IA/0005/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.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.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	22/06/2018	n/a		
T/0003	Transfer of Marketing Authorisation	20/03/2018	30/04/2018	SmPC, Labelling and PL	
II/0002	Update of sections 4.5 and 5.2 of the SmPC in order to reflect the results from study R1701192 "In vitro assessment of cytochrome P450 3A4 and 3A5	26/04/2018	17/04/2019	SmPC	

	enzyme inhibition by midostaurin, CGP52421 and CGP62221" and update of section 5.2 of the SmPC to reflect the results from study R1600721 "Assessment of midostaurin and its metabolites (CGP052421 and CGP062221) as inhibitors of human bile salt export pump (BSEP)", in fulfilment of the post-authorisation measures MEA 011 and REC 014. In addition, the MAH took the opportunity to update section 5.2 to correct figures, to amend a minor typographical error in section 4.2 of the SmPC, as well as to align information regarding women of childbearing potential in section 4.6 of the SmPC with section 4.4. The RMP version 2.2 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0001	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	15/11/2017	30/04/2018	SmPC, Labelling and PL	