# Komboglyze

## 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 |
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| WS/2544 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on 'Vitamin B12 decrease/deficiency' and to change the frequency of | 08/02/2024 | | SmPC and PL | Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be |

[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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| | 'Vitamin B12 decrease/deficiency' in the list of adverse drug reactions (ADRs) from frequency 'very rare' to 'common'. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the contact details of the local representative in the Netherlands in the Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines. |
| IG/1624 | B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS | 30/10/2023 | n/a | | |
| IA/0056 | 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) | 22/06/2023 | n/a | | |
| IAIN/0055 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release | 30/05/2023 | | Annex II and PL | |
| N/0054 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 06/12/2022 | | PL | |
| PSUSA/2686/ | Periodic Safety Update EU Single assessment - | 07/07/2022 | n/a | | PRAC Recommendation - maintenance |

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| 202111 | metformin / saxagliptin | | | | |
| IA/0052/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites | 02/12/2021 | 13/04/2022 | Annex II and PL | |
| WS/2098 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Submission of the final report from study D1680C00016 (MEASURE HF) (listed as a category 3 study in the RMP). This is a 24-week, multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the effects of saxagliptin and sitagliptin on cardiac dimensions and function in patients with Type 2 Diabetes Mellitus and Heart Failure. The updated combined RMP version 16 for Komboglyze and Onglyza was agreed during the procedure.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 02/12/2021 | n/a | | n/a |
| IG/1358/G | This was an application for a group of variations. | 03/03/2021 | 13/04/2022 | Annex II and | |

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| | A.7 - Administrative change - Deletion of manufacturing sites<br>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 | | | PL | |
| WS/1975 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 14/01/2021 | n/a | | |
| IA/0048 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 28/08/2020 | n/a | | |
| WS/1743 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.4 of the SmPC in order to add a new warning about Bullous pemphigoid and section 4.8 of the SmPC to include Bullous pemphigoid as a new ADR with a frequency of 'Not known'. The Package Leaflet has been updated accordingly. | 12/03/2020 | 09/03/2021 | SmPC and PL | Based on all available data (literature publications, postmarketing cases and biological plausibility) there is a probable causal relationship between the use of saxagliptin-containing products and Bullous pemphigoid. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| II/0046 | Submission of an updated RMP version 15 in order to implement the revised GVP template Rev.2. As a result, the list of safety concerns has been revised and a number of important identified risks, important potential risks and missing information have been reclassified and have been removed from the RMP.<br><br>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 | 11/07/2019 | n/a | | n/a |
| PSUSA/2686/ 201811 | Periodic Safety Update EU Single assessment - metformin / saxagliptin | 14/06/2019 | n/a | | PRAC Recommendation - maintenance |
| IB/0045/G | This was an application for a group of variations.<br><br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation<br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation<br>B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the | 06/05/2019 | n/a | | |

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| | relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | | | | |
| WS/1289 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to reflect the new saxagliptin renal cut-off value based on post hoc analysis of pooled data from 9 saxagliptin clinical trials. In addition, the Worksharing applicant combined the SmPCs of different strengths, for both Onglyza and Komboglyze. Furthermore, the Worksharing applicant took the opportunity to include required information on two excipients, sodium and lactose, in sections 2 and 4.4 of the SmPC for Onglyza. The Package Leaflet is updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 28/06/2018 | 13/08/2018 | SmPC and PL | No dose adjustment is recommended for patients with mild renal impairment or in patients with moderate renal impairment that have GFR ≥ 45 mL/min. The dose should be reduced to 2.5 mg once daily in patients with moderate renal impairment that have GFR < 45 mL/min and in patients with severe renal impairment. |
| IG/0934 | A.7 - Administrative change - Deletion of manufacturing sites | 15/06/2018 | n/a | | |
| PSUSA/2686/ 201711 | Periodic Safety Update EU Single assessment - metformin / saxagliptin | 14/06/2018 | n/a | | PRAC Recommendation - maintenance |
| IB/0042/G | This was an application for a group of variations. | 06/06/2018 | n/a | | |

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| | 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<br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>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 originally approved batch size<br>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 originally approved batch size<br>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 originally approved batch size<br>B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits<br>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<br>B.I.b.1.c - Change in the specification parameters | | | | |

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| | and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method<br>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<br>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)<br>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)<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters | | | | |

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| | and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | | | | |
| IG/0892 | 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 | 28/02/2018 | n/a | | |
| IG/0862 | 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 | 24/10/2017 | n/a | | |
| WS/1078 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | 18/05/2017 | 26/06/2017 | SmPC, Labelling and PL | |
| PSUSA/2686/ 201611 | Periodic Safety Update EU Single assessment - metformin / saxagliptin | 09/06/2017 | n/a | | PRAC Recommendation - maintenance |
| WS/0960/G | This was an application for a group of variations following a worksharing procedure according to | 18/05/2017 | n/a | | Based on the review of five epidemiological studies evaluating each risk and literature data for acute kidney |

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| | Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Group of variations consisting of final epidemiological results for 1) D1680R00011 study related to risk of infection), 2) D1680R00012 study related to risk of severe hypersensitivity,3) D1680R00013 study related to risk for acute kidney injury, 4) D1680R00014 study related to acute liver failure, 5) D1680R00015 study related to major cardiovascular events and 6) update of the RMP to reflect the submission of the 5 epidemiological studies. As a consequence, the RMP (Onglyza: version 12, Komboglyze: version 13) is updated accordingly. In addition, routine changes are made in parts III (pharmacovigilance plan, overview of planned pharmacovigilance actions) and IV. A safety review based on literature has also been included to investigate acute kidney injury associated with saxagliptin/saxagliptin and metformin at the PRAC request.<br>The requested grouped worksharing procedure proposed amendments to the Risk Management Plan (RMP).<br><br>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<br>C.I.13 - Other variations not specifically covered | | | | injury, no increased risk for hospitalisation for infection, for severe hypersensitivity events, for acute kidney injury, for acute liver failure, for major cardiovascular events was observed, when initiating treatment with saxagliptin. The submitted RMPs were approved (Onglyza : version 12, Komboglyze : version 13). |

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| | elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | | | | |
| IB/0036 | C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority | 20/04/2017 | n/a | | |
| A31/0030 | Pursuant to Article 31 of Regulation (EC) No 726/2004, the European Commission requested on 25 January 2016 the opinion of the European Medicines Agency on the adequacy of the current recommendations for metformin containing products with respect to the use in patients with moderate renal failure, taking into account the available information on the risk of lactic acidosis. The CHMP was requested to assess the impact thereof on the benefit-risk balance of metformin containing products and to give its recommendation whether | 13/10/2016 | 12/12/2016 | SmPC and PL | Please refer to the assessment report:<br>Metformin containing medicinal products - EMEA/H/A-31/1432 |

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| | the marketing authorisation of this product should be maintained, varied, suspended or revoked.<br>The notification for the procedure is appended to this opinion. | | | | |
| R/0032 | Renewal of the marketing authorisation. | 26/05/2016 | 15/07/2016 | SmPC, Annex II, Labelling and PL | Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Komboglyze in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. |
| IB/0034/G | This was an application for a group of variations.<br><br>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<br>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<br>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<br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other | 14/07/2016 | n/a | | |

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| | variation | | | | |
| PSUSA/2686/ 201511 | Periodic Safety Update EU Single assessment - metformin / saxagliptin | 09/06/2016 | n/a | | PRAC Recommendation - maintenance |
| WS/0902 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 5.1 of the SmPC, upon request by the CHMP following the assessment of the post-authorisation measures LEG 038.1 (Onglyza) and LEG 015.1 (Komboglyze), with information regarding effect on all-cause mortality. In addition, the MAH took the opportunity to implement minor editorial changes in the Package Leaflet and to update the contact information for the local representative in Poland in the Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 28/04/2016 | 15/07/2016 | SmPC and PL | In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction (SAVOR) Study, no benefit was observed for MACE or all-cause mortality. The secondary endpoint, all-cause mortality, occurred at a rate of 5.1% in the saxagliptin group and 4.6% in the placebo group. CV deaths were balanced across the treatment groups. There was a numerical imbalance in non-CV death, with more events on saxagliptin (1.8%) than placebo (1.4%) [HR = 1.27; (95% CI 1.00, 1.62); P = 0.051]. |
| WS/0897 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Submission of a final clinical study report for an epidemiological study CV181-102 with the aim to assess risk factors associated with low lymphocyte count in patients with T2DM (PASS study category 3 | 01/04/2016 | n/a | | |

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| | currently in the RMP) together with an updated RMP v.10.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | | | | |
| WS/0839 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 17/12/2015 | n/a | | |
| IG/0633 | 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 | 09/12/2015 | n/a | | |
| WS/0851/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation<br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 19/11/2015 | n/a | | |

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| | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation<br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation<br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | | | | |
| WS/0810/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 01/10/2015 | 15/07/2016 | SmPC, Labelling and PL | |
| IG/0601 | 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) | 09/09/2015 | n/a | | |
| PSUSA/2686/ 201411 | Periodic Safety Update EU Single assessment - metformin / saxagliptin | 25/06/2015 | 14/08/2015 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2686/201411. |

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| IG/0576 | B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer | 26/06/2015 | n/a | | |
| IAIN/0021/G | This was an application for a group of variations.<br><br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>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<br>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<br>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 - | 20/05/2015 | 14/08/2015 | Annex II and PL | |

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| | Not including batch control/testing<br>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<br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | | | | |
| IG/0522 | 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 | 12/03/2015 | n/a | | |
| PSUV/0017 | Periodic Safety Update | 04/12/2014 | n/a | | PRAC Recommendation - maintenance |
| T/0018 | Transfer of Marketing Authorisation from Bristol-Myers Squibb/AstraZeneca EEIG to AstraZeneca AB.<br><br>Transfer of Marketing Authorisation | 23/09/2014 | 15/10/2014 | SmPC, Labelling and PL | |
| WS/0529/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC with regard to posology recommendations and warnings for use in elderly patients and patients with renal impairment, minor amendment of the existing | 24/07/2014 | 15/10/2014 | SmPC and PL | Regarding the use of Komboglyze and Onglyza in older patients, no dose adjustment is recommended based solely on age.<br>No dose adjustment is recommended for patients with mild renal impairment. The dose should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment. Onglyza is not recommended for patients with end stage renal disease (ESRD) requiring haemodialysis. Experience in NYHA class III-IV of heart failure is still |

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| | warning on skin disorders, lack of inhibition of CYP2C8 by saxagliptin and inclusion of safety and efficacy information from study D1680C00003 (SAVOR), a cardiovascular outcome study, and study D1680L00002 (GENERATION), a study comparing saxagliptin with glimepiride in elderly patients. Furthermore, the MAH took the opportunity to implement QRD version 9 for Komboglyze and to update the list of local representatives and to perform minor editorial corrections throughout both PIs.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | limited. Therefore, caution is warranted in these patients.<br>In the SAVOR trial a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo (see section 5.1). Additional analysis did not indicate a differential effect among NYHA classes.<br>In in vitro studies, saxagliptin and its major metabolite did not inhibit CYP2C8.<br>SAVOR was a cardiovascular outcome study conducted in 16,492 patients with type II diabetes who had a history of, or were at risk for, cardiovascular events. Its results demonstrated that saxagliptin is non-inferior to placebo and does not induce an increased risk for cardiovascular death, non-fatal myocardial infarction or non-fatal ischaemic stroke.<br>GENERATION was a 52-week trial performed in 720 elderly patients. The purpose was to evaluate whether saxagliptin + Metformin was superior to glimepiride + metformin on the primary endpoint of subjects reaching HbA1c < 7% without hypoglycaemia (confirmed or severe). There appeared to be no difference in responders. Glimepiride was more effective than saxagliptin in reducing HbA1c, but at the cost of more hypoglycaemia. Saxagliptin was less effective, but can still reduce HbA1c to some extent, and did not induce hypoglycaemia. Age appeared to be an important factor: results favoured saxagliptin in subjects < 75, and glimepiride in subjects > 75 years. |
| WS/0528 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. | 26/06/2014 | 15/10/2014 | SmPC and PL | In this variation the Product information of Komboglyze and Onglyza has been updated with additional information related to the use of these products in patients with history of pancreatic disease and with advice on seeking medical |

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| | Update of section 4.4 of the SmPC in order to implement the recommendations of an Art 5(3) procedure on GLP-1-based therapies and pancreatic safety.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | | | | help in cases of signs and symptoms of pancreatitis. |
| PSUV/0016 | Periodic Safety Update | 12/06/2014 | n/a | | PRAC Recommendation - maintenance |
| N/0013 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 11/11/2013 | 15/10/2014 | PL | |
| WS/0416/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>To add an alternate manufacturer of the active substance Saxagliptin and intermediates<br>To increase the maximum batch size of an intermediate<br>To increase the maximum batch size of the active substance Saxagliptin<br><br>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<br>B.I.a.3.a - Change in batch size (including batch size | 19/09/2013 | n/a | | |

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| | ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size<br>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 | | | | |
| IA/0012 | B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size | 08/07/2013 | n/a | | |
| IG/0259 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 18/01/2013 | n/a | | |
| WS/0295 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the indication for Onglyza and Komboglyze to include combination of metformin, a suphonylurea and saxagliptin, i.e. triple oral therapy. The Package Leaflet and Labelling are updated accordingly.<br>Furthermore, the PI is being brought in line with the latest QRD template version 8.2.<br>Furthermore, in the SmPC and the Package Leaflet minor typographical errors were corrected and these were harmonized for the two products. | 17/01/2013 | 18/02/2013 | SmPC, Annex II, Labelling and PL | For further information please refer to the scientific conclusion: H-2059-VAR-WS-295-en for Komboglyze and H-1039-VAR-WS-295-en for Onglyza. |

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| | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | | | | |
| IB/0008 | 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) | 04/01/2013 | 18/02/2013 | SmPC | |
| II/0004 | Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the indication for combination of Komboglyze with insulin (i.e., triple combination therapy). The Package Leaflet is updated in accordance.<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | 20/09/2012 | 24/10/2012 | SmPC and PL | For further information please refer to the scientific conclusion: H-2059-VAR-II-0004-en. |
| IB/0005 | 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 | 26/09/2012 | n/a | | |
| IA/0007 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 01/08/2012 | n/a | | |
| IB/0003 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 10/05/2012 | n/a | | |

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| IA/0002 | 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 | 03/04/2012 | n/a | | |
| IB/0001/G | This was an application for a group of variations.<br><br>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<br>B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes<br>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 | 27/02/2012 | 24/09/2012 | SmPC, Annex II, Labelling and PL | |