# Xeloda

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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| PSUSA/531/202404 | Periodic Safety Update EU Single assessment - capecitabine | 30/01/2025 | 28/03/2025 | SmPC | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/531/202404. |
| IB/0101 | B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement | 24/04/2024 | n/a | | |

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

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| | or addition) for the AS or a starting material/intermediate | | | | |
| IA/0100 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 07/03/2024 | n/a | | |
| IAIN/0099/G | This was an application for a group of variations.<br><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.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 | 25/10/2022 | 12/10/2023 | Annex II and PL | |
| T/0098 | Transfer of Marketing Authorisation | 24/06/2022 | 08/07/2022 | SmPC, Labelling and PL | |
| PSUSA/531/202104 | Periodic Safety Update EU Single assessment - capecitabine | 02/12/2021 | n/a | | PRAC Recommendation - maintenance |
| IB/0096 | B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation | 27/10/2021 | n/a | | |
| IA/0097 | A.7 - Administrative change - Deletion of | 27/09/2021 | n/a | | |

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| | manufacturing sites | | | | |
| N/0094 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/08/2021 | 08/07/2022 | PL | |
| IB/0092 | C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation | 05/07/2021 | 08/07/2022 | SmPC and PL | |
| IA/0093 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 03/05/2021 | n/a | | |
| IAIN/0091 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 26/02/2021 | 27/05/2021 | SmPC, Annex II, Labelling and PL | |
| IA/0090 | 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) | 28/07/2020 | n/a | | |
| A31/0085 | Pursuant to Article 31 of Directive 2001/83/EC, France requested on 13 March 2019 the opinion of the European Medicines Agency to assess the need to take action at EU level regarding the detection of DPD deficient patients (especially through genotyping and/or phenotyping) in patients treated with fluorouracil and related substances (capecitabine, tegafur and flucytosine). The Agency was requested to assess the impact thereof on the | 30/04/2020 | 03/07/2020 | SmPC and PL | Please refer to the assessment report: Xeloda EMEA/H/A-31/1481/C/000316/0085 |

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| | benefit-risk balance of fluorouracil and related substances containing products and to give its opinion on whether the marketing authorisation of these products should be maintained, varied, suspended or revoked. | | | | |
| IB/0089 | B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product | 03/06/2020 | 27/05/2021 | SmPC, Labelling and PL | |
| IB/0088 | B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation | 27/09/2019 | n/a | | |
| IA/0087 | A.7 - Administrative change - Deletion of manufacturing sites | 22/07/2019 | n/a | | |
| II/0083 | Update of section 4.6 of the SmPC in order to add advice on post treatment female and male contraception period and wash out period before initiation of breastfeeding. 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 | 27/06/2019 | 03/07/2020 | SmPC and PL | An effective method of contraception should be used during treatment and for 6 months after the last dose of capecitabine. Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of capecitabine.<br>No studies have been conducted to assess the impact of capecitabine on milk production or its presence in human breast milk. As the potential for harm to the nursing infant is unknown, breast-feeding should be discontinued while receiving treatment with capecitabine and for 2 weeks after the final dose. |

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| II/0081 | Update of sections 4.2, 4.4, 4.8 and 6.6 of the SmPC in relation to cutting or crushing of Xeloda tablets. The Package Leaflet is updated accordingly. In addition, the MAH is taking the opportunity to make some editorial changes to the Product Information.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 26/04/2019 | 27/05/2019 | SmPC and PL | Xeloda tablets should be swallowed whole with water within 30 minutes after a meal. Xeloda tablets should not be crushed or cut. In case of exposure of either patient or caregiver to crushed or cut Xeloda tablets adverse drug reactions could occur as follows: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhoea, nausea, gastric irritation and vomiting. |
| IA/0086 | 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) | 10/04/2019 | n/a | | |
| PSUSA/531/201804 | Periodic Safety Update EU Single assessment - capecitabine | 31/01/2019 | 28/03/2019 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/531/201804. |
| IAIN/0084/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.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.1.b - Replacement or addition of a | 21/03/2019 | n/a | | |

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| | manufacturing site for the FP - Primary packaging site<br>B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised | | | | |
| IB/0082/G | This was an application for a group of variations.<br><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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation | 22/02/2019 | n/a | | |
| II/0077 | 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 | 06/09/2018 | n/a | | |
| N/0079 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/08/2018 | 28/03/2019 | PL | |
| IA/0078/G | This was an application for a group of variations.<br><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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process | 03/08/2018 | n/a | | |

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| | 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.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.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | | | | |
| II/0074 | Update of section 4.4 of the SmPC with regards to DPYD genotyping, following a request from the PRAC after assessment of LEG 033.1.<br><br>C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH | 22/03/2018 | 28/03/2019 | SmPC | Patients with certain heterozygous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variant) have been shown to have increased risk of severe toxicity when treated with capecitabine.<br>The frequency of the heterozygous DPYD*2A genotype in the DYPD gene in Caucasian patients is around 1%, 1.1% for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0.07 to 0.1% for c.1679T>G Genotyping for these alleles is recommended to identify patients at increased risk for severe toxicity. Data on the frequency of these DPYD variants in other populations than Caucasian is limited. It cannot be excluded that other rare variants may also be associated with an increased risk of severe toxicity.<br>For patients with partial DPD deficiency (such as those with |

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| | | | | | heterozygous mutations in the DPYD gene) and where the benefits of Xeloda are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution and frequent monitoring with dose adjusment according to toxicity. A reduction of the starting dose in these patients may be considered to avoid serious toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test. It has been reported that the DPYD*2A, c.1679T>G variants lead to a greater reduction in enzymatic activity than the other variants with a higher risk of side effects. The consequences of a reduced dose for efficacy are currently uncertain. Therefore, in the absence of serious toxicity the dose could be increased while carefully monitoring the patient.<br>The patients who are tested negative for the above-mentioned alleles may still have a risk of severe adverse events. |
| T/0076 | Transfer of Marketing Authorisation | 20/02/2018 | 16/03/2018 | SmPC, Labelling and PL | |
| IA/0075 | 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 | 11/01/2018 | n/a | | |
| IB/0072/G | This was an application for a group of variations. | 05/10/2017 | n/a | | |

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| | 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<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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold<br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation | | | | |
| IB/0073/G | This was an application for a group of variations.<br><br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.d.2.z - Change in test procedure for the finished product - Other variation | 20/07/2017 | n/a | | |
| IA/0071 | 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 | 26/04/2017 | n/a | | |
| II/0070 | Update of sections 4.4 and 4.8 of the SmPC in order to include a warning on fingerprint loss. The Package | 23/06/2016 | 10/07/2017 | SmPC, Annex II, Labelling | |

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| | Leaflet is updated accordingly. The RMP version 9.0 is also agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the QRD template version 10.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | and PL | |
| PSUSA/531/201504 | Periodic Safety Update EU Single assessment - capecitabine | 03/12/2015 | n/a | | PRAC Recommendation - maintenance |
| II/0067 | Update of sections 4.3 and 4.4 of the SmPC in order to modify the wording of the contraindication regarding patients with known dihydropyrimidine dehydrogenase (DPD) deficiency and to add information about warnings and precautions regarding patients with DPD deficiency. The Package Leaflet is updated accordingly. In addition the MAH is deleting one of the conditions related to the submission of the RMP in Annex II.<br>The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet, Annex II and the Risk Management Plan (RMP).<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 24/09/2015 | 14/01/2016 | SmPC, Annex II and PL | Update of sections 4.3 and 4.4 of the SmPC in order to modify the wording of the contraindication regarding patients with known dihydropyrimidine dehydrogenase (DPD) deficiency and to add information about warnings and precautions regarding patients with DPD deficiency. The Package Leaflet is updated accordingly. In addition the MAH is deleting one of the conditions related to the submission of the RMP, as a result Annex II is also being updated. |

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| IG/0573 | 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 | 01/07/2015 | n/a | | |
| IB/0066/G | This was an application for a group of variations.<br><br>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<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure<br>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<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 13/02/2015 | n/a | | |
| II/0064 | Update of section of section 4.8 of the SmPC to add the adverse reaction toxic leukoencephalopathy reported in the post-marketing experience with "Very Rare" frequency. Adverse reactions listed from the post-marketing experience have also been integrated into the relevant tables reporting adverse reactions when used in monotherapy or combination therapy in line with a request from the CHMP. The MAH also took the opportunity to make editorial corrections. | 22/01/2015 | 14/01/2016 | SmPC | Cases of toxic leukoencephalopathy have been reported in the post-marketing experience with capecitabine; in particular, in 10 of 40 cases of leukoencephalopathy the role of capecitabine can be considered as possible in causing this adverse event as all of these 10 cases demonstrated positive rechallenge. Therefore toxic leukoencephalopathy (not virus associated) is considered a very rare adverse drug reaction. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| PSUSA/531/201404 | Periodic Safety Update EU Single assessment - capecitabine | 04/12/2014 | n/a | | PRAC Recommendation - maintenance |
| IG/0497 | 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 | 18/11/2014 | n/a | | |
| II/0060 | 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 | 25/09/2014 | n/a | | |
| IB/0062 | 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 | 05/08/2014 | n/a | | |
| IA/0061 | B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold | 16/06/2014 | n/a | | |
| N/0059 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 04/03/2014 | 15/12/2014 | PL | |

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| II/0058 | Submission under article 46 of paediatric regulation (EC) no 1901/2006 of the NO21125 final study report on capecitabine and concomitant radiation therapy in children with newly diagnosed brainstem gliomas.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 23/01/2014 | n/a | | Please refer to the Scientific Discussion Xeloda-H-C-316-II-58 |
| II/0057/G | This was an application for a group of variations.<br><br>Update of section 4.4 of the SmPC with regard to prophylactic treatment of hand-foot syndrome, as recommended in conclusion to the assessment of the latest PSUR 10 (PSU 027). In addition, section 4.5 of the SmPC is updated with regard to interaction with folinic/folic acid upon switching from 5 fluorouracil to capecitabine, as recommended in conclusion to the assessment of PSUR 8.The Package Leaflet is updated accordingly. In addition, minor amendments are made to the SmPC and to the Package Leaflet.<br><br>C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH<br>C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the | 23/01/2014 | 15/12/2014 | SmPC and PL | Hand-foot syndrome, also known as hand-foot skin reaction or palmar-plantar erythrodysaesthesia or chemotherapy induced acral erythema is a known adverse drug reaction of Xeloda treatment. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Xeloda.<br>Folinic acid, and folic acid due to the similarity between the two, have an effect on the pharmacodynamics of capecitabine and the toxicity of capecitabine may be enhanced by folinic/folic acid. The enhanced toxicity may be relevant when switching from 5-FU/LV to a capecitabine regimen. This may also be relevant with folic acid supplementation for folate deficiency. |

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| | assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH | | | | |
| II/0055 | Update of section 4.4 of the SmPC to include acute renal failure as complication of dehydration due to Xeloda treatment and of section 4.8 of the SmPC to include acute renal failure secondary to dehydration as an Adverse Drug Reaction (ADR) of Xeloda therapy in follow-up to the assessment of a relevant Eudravigilance signal. The Package Leaflet is updated accordingly. In addition, minor changes are made to section 5.1 of the SmPC.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 18/12/2013 | 15/12/2014 | SmPC and PL | Based on a review of the safety database performed by the MAH, which revealed a number of cases of acute renal failure secondary to dehydration developing in the course of Xeloda treatment, the CHMP considered that an association between acute renal failure secondary to dehydration and capecitabine use was likely. Dehydration developing during Xeloda treatment may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic drugs. Acute renal failure secondary to dehydration might be potentially fatal. |
| II/0054 | Update of section 5.1 of the SmPC with updated efficacy and safety information for XELIRI (CAPIRI) and new efficacy and safety information specifically for XELIRI (CAPIRI) +/- bevacizumab and of sections 4.4 and 4.8 in order to include a warning and information on severe skin reactions as adverse drug reactions of Xeloda, respectively, following PRAC recommendations further to the assessment of PSUR 10 (PSU 027). In addition, section 4.2 of the SmPC is updated in order to include additional dose recommendations on the combination with irinotecan. The Package Leaflet is updated accordingly.<br><br>C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure | 21/11/2013 | 18/12/2013 | SmPC and PL | In metastatic colorectal cancer, the efficacy of XELIRI (capecitabine+irinotecan) regimens is similar to that of FOLFIRI (5 fluorouracil+irinotecan) regimens and modified XELIRI regimens (employing lower doses of capecitabine and irinotecan) are not associated with loss of efficacy. Although studies which have included XELIRI +/- bevacizumab have shown variable results with respect to efficacy and toxicity, tolerance to treatment may be improved by modifying (dose reduction) the capecitabine and irinotecan doses used. Although the regimen using capecitabine 1000mg/m2 bid + irinotecan 250mg/m2 is the most frequently used one, the optimal dose combination has not been established. For combination with irinotecan, the recommended starting dose of Xeloda is 800 mg/m2 when administered twice daily for 14 days followed by a 7-day rest period combined with irinotecan 200 mg/m2 on |

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| | concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH | | | | day 1.<br>In addition, severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported as very rare adverse reactions during Xeloda treatment. Xeloda should be permanently discontinued in patients who experience a severe skin reaction. |
| IA/0056 | A.7 - Administrative change - Deletion of manufacturing sites | 14/10/2013 | n/a | | |
| II/0053 | Update of sections 4.4 and 4.8 of the SmPC in order to add a warning regarding ophthalmologic complications and to include corneal disorders, keratitis, punctate keratitis and cutaneous lupus erythematosus as adverse drug reactions during Xeloda treatment as requested by CHMP following the assessment of PS2 024.1. The Package Leaflet is updated accordingly. Minor editorial amendments are made to the SmPC and Package Leaflet. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet with the addition of the Croatian representative. Furthermore, the PI is being brought in line with the latest QRD template version 9.0.<br><br>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 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | 30/05/2013 | 29/11/2013 | SmPC, Annex II and PL | Following relevant rare cases reported in the post-marketing setting, ophthalmologic complications (corneal disorders, keratitis, punctate keratitis) and cutaneous lupus erythematosus were included in the list of adverse drug reactions of Xeloda in section 4.8 of the SmPC. In addition, a warning has been included in section 4.4 of the SmPC highlighting that patients should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate. The package leaflet was updated accordingly. |

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| IA/0052/G | This was an application for a group of variations.<br><br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | 13/12/2012 | n/a | | |
| IG/0228 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 23/11/2012 | n/a | | |
| II/0049 | Update of sections 4.2 and 4.4 of the SmPC in order to include wording related to DPD deficiency in follow up to the assessment of PSUR 9. Moreover, section 4.5 of the SmPC is updated with regard to interaction with cytochrome P450 substrates and radiation recall syndrome is added as a new Adverse Drug Reaction in section 4.8 of the SmPC. Minor changes are made to the SmPC and Package Leaflet (PL) including changes to sections 4.2, 4.6 and 5.1 in line with the SmPC Guideline. The PL is updated accordingly and it is extensively revised to reflect information in the SmPC. 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 QRD template version 8.1 (July 2011).<br><br>C.I.3.b - Implementation of change(s) requested | 15/11/2012 | 29/11/2013 | SmPC, Annex II, Labelling and PL | Severe toxicities have rarely been reported in patients treated with 5-FU, which have been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD). Patients with known DPD deficiency should not be treated with capecitabine (Xeloda), a pro-drug of 5-FU. Careful monitoring during the first cycle of treatment is recommended for all patients. In patients with unrecognised DPD deficiency treated with Xeloda, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately until toxicity resolves and permanent discontinuation should be considered.<br>Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is co-administered with 2C9 substrates (e.g., phenytoin).<br>Finally, radiation recall syndrome has uncommonly been |

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| | following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | | | | reported with capecitabine in the scientific literature. |
| A20/0048 | Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 December 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the manufacturing site Roche Carolina Inc. (RCI), Florence, in the United States of America (USA), to assess the impact thereof on the risk-benefit balance of Xeloda and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn. | 19/07/2012 | 20/09/2012 | | Please refer to the assessment report : EMEA/H/C/316/A-20/0048 |
| N/0050 | Update the contact telephone number for Roche, France in the Package leaflet.<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 11/09/2012 | 29/11/2013 | PL | |
| II/0047 | Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SmPC) in order to revise the wording related to cardiotoxicity as requested by the CHMP further to the assessment of cardiac safety signals identified in the Eudravigilance database. | 19/05/2011 | 17/06/2011 | SmPC, Annex II and PL | Following cases of QT prolongation, torsades de point, ventricualr fibrillation and bradycardia reported with Xeloda in Eudravigilance and a relevant review in the Marketing Authorisation Holder's safety database, these terms were added in the list of Adverse Drug Reactions of Xeloda in |

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| | In addition, the MAH took the opportunity to update section 4.6 of the SmPC and Annex II to bring them in line with the current QRD template and to make editorial changes to the Package Leaflet.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | section 4.8 of the SmPC with a reported frequency very rare. The relevant wording on cardiaotoxicity in section 4.4 of the SmPC was also amended to include these terms as examples of electrocardiographic changes/arrythmias. |
| II/0043 | Addition of an alternative manufacturing site.<br><br>Quality changes | 22/07/2010 | 04/08/2010 | | |
| IA/0046 | A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) | 21/07/2010 | n/a | | |
| IB/0045/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS<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.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of | 09/06/2010 | n/a | | |

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| | specification limits<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.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<br>B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS | | | | |
| II/0044 | Update of sections 4.2, 4.8 and 5.1 of the SPC to include the safety and efficacy results from the pivotal study NO16968 and the final results of the meta-analysis requested at the time of the extension of indication in advanced gastric cancer. The MAH also took the opportunity to perform minor editorial amendments and update the list of local representatives in the Package Leaflet, as well as to revise Annex II with information on the Risk Management Plan according to the latest QRD template.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 18/02/2010 | 23/03/2010 | SmPC, Annex II and PL | The MAH submitted an additional clinical study (NO16968) on the combination of capecitabine with oxaliplatin in the adjuvant treatment of colon cancer. The MAH further fulfilled all post authorisation commitments undertaken at the time of the extension of indication in advanced gastric cancer including meta-analyses involving all submitted gastrointestinal cancer studies. Section 4.2 of the SPC has been updated to include recommendations regarding combination therapy in the adjuvant treatment of colon cancer and recommendations specific to the combination with oxaliplatin. Section 5.1 has been updated with efficacy data from the combination trial in the adjuvant treatment of colon cancer. Sections 4.8 and 5.1 have also been updated to reflect the results of study NO 16968 and of the updated meta-analyses. |
| IB/0041 | IB_10_Minor change in the manufacturing process of | 23/07/2009 | n/a | | |

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| | the active substance | | | | |
| IB/0040 | IB_38_c_Change in test procedure of finished product - other changes | 16/06/2009 | n/a | | |
| IA/0039 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 02/06/2009 | n/a | | |
| IB/0036 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 14/04/2009 | n/a | | |
| II/0035 | Changes in the synthetic process of the active substance.<br><br>Update of or change(s) to the pharmaceutical documentation | 19/03/2009 | 03/04/2009 | | |
| IA/0038 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 26/03/2009 | n/a | | |
| IA/0037 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 26/03/2009 | n/a | | |
| II/0034 | Update of sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SPC to fulfil the Clinical Follow Up Measure to provide the results of the safety meta-analysis, including studies NO16966 and NO16967. The Package Leaflet has been amended accordingly.<br><br>Update of Summary of Product Characteristics and | 25/09/2008 | 31/10/2008 | SmPC and PL | This variation has resulted in a condensed and easier to reproduce display of the relevant information (specifically as regards to sec. 4.8) of the SPC of Xeloda 150 and 500 mg Film-coated tablets.<br><br>The requested and performed meta-analysis did clarify several issues and question of the past, or provided further |

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| | Package Leaflet | | | | insights into phenomena observed. The information relevant for the prescriber deriving from this analysis are contained in the revised SPC, section 4.5.<br><br>The concerns also ultimately confirmed in the multi-factorial Cox regression analysis (submitted with the responses), is that starting dose is seemingly more relevant than e.g. cumulative dose for the outcome of the patient. This is, however, the result of a meta-analysis. Concerning dose recommendations/recommendations for dose adjustments, these are derived from the results of single trials in a pre-specified population (i.e., on the "history" of the currently licensed posology as of section 4.2). |
| II/0033 | The MAH applied to update section 5.1 of the SPC to include the long-term efficacy data based on the 5 year results for disease-free survival (DFS) and overall survival (OS) from study M66001 (X-ACT) following the completion of a clinical FUM.<br><br>Update of Summary of Product Characteristics | 21/02/2008 | 27/03/2008 | SmPC | The positive benefit-risk assessment as concluded when Xeloda was assessed for the adjuvant indication in colon cancer stage III is now reconfirmed by the data after patients had been followed up for 5 years as part of the commitments of the Marketing Authorisation Holder. In addition, these new data confirm that 3 year DFS in colon cancer stage III treated with surgery and adjuvant chemotherapy predicts 5 year OS as already postulated in several preceding publications.<br><br>Xeloda was shown to be superior to bolus 5-FU/LV in a pre-planned multivariate Cox analysis therefore, the data for disease free survival (HR = 0.849 [95% CI: 0.739 - 0.976], p = 0.0212), as well as for overall survival (HR = 0.828 [95% CI: 0.705 - 0.971], p = 0.0203) were added in section 5.1.<br>Furthermore, in the light of the increasing role of FOLFOX in the adjuvant treatment of colon cancer stage II-III, it |

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| | | | | | was suggested to further improve the SPC by clearly giving the information in sec. 5.1 that experience with adjuvant Xeloda combination therapy in colon cancer stage (II-) III is currently lacking. |
| II/0028 | Widening of the current indication to: "Xeloda is indicated for the treatment of metastatic colorectal cancer". The MAH took the opportunity to update the contact details of the local representations of Estonia and Finland in the Package Leaflet.<br><br>Extension of Indication | 13/12/2007 | 31/01/2008 | SmPC, Annex II, Labelling and PL | Please refer to the Scientific Discussion for further information. |
| IA/0032 | IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms | 13/12/2007 | n/a | SmPC | |
| IB/0029 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 19/09/2007 | n/a | | |
| IA/0030 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 20/07/2007 | n/a | | |
| IB/0026 | IB_10_Minor change in the manufacturing process of the active substance | 02/04/2007 | n/a | | |
| IB/0025 | IB_10_Minor change in the manufacturing process of the active substance | 02/04/2007 | n/a | | |
| II/0018 | The MAH applied to extend the indication to include "Xeloda is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen". The MAH has also applied | 22/02/2007 | 28/03/2007 | SmPC, Annex II, Labelling and PL | Please refer to Scientific Discussion for further information. |

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| | to revise section 4.8 of the SPC regarding Post-Marketing Experience, to update the Labelling section 16. "Information in Braille" and to update the Package Leaflet according to the latest QRD template.<br><br>Extension of Indication | | | | |
| IA/0027 | IA_13_a_Change in test proc. for active substance - minor change | 23/01/2007 | n/a | | |
| IB/0019 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 14/12/2006 | n/a | | |
| IA/0024 | IA_32_a_Change in batch size of the finished product - up to 10-fold | 14/12/2006 | n/a | | |
| IB/0021 | Modules 1, 2 and 3<br><br>IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 14/11/2006 | n/a | | |
| IA/0023 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 20/10/2006 | n/a | | |
| IA/0022 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 20/10/2006 | n/a | | |
| IA/0020 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 16/10/2006 | n/a | Annex II and PL | |

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| II/0017 | Update of Summary of Product Characteristics and Package Leaflet | 27/04/2006 | 31/05/2006 | SmPC and PL | The MAH applied for revisions of section 4.8 "Undesirable effects" of the SPC to minimize redundancies in the section "uncommon adverse events" and section 4.2 "Posology and Method of Administration" in order to specify the posology for each of the indications of Xeloda. Amendments of the contact details for the local representative in Latvia were also implemented in the Package Leaflet. |
| R/0015 | Renewal of the marketing authorisation. | 14/12/2005 | 09/02/2006 | SmPC, Annex II, Labelling and PL | |
| IA/0016 | IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases | 13/01/2006 | n/a | | |
| II/0012 | Update of or change(s) to the pharmaceutical documentation | 13/10/2005 | 20/10/2005 | | |
| IA/0014 | IA_01_Change in the name and/or address of the marketing authorisation holder | 03/10/2005 | n/a | SmPC, Labelling and PL | |
| IA/0013 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold | 08/08/2005 | n/a | | |
| II/0009 | Extension of Indication | 17/02/2005 | 30/03/2005 | SmPC and PL | To extend the indication for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. |
| IA/0011 | IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 04/03/2005 | n/a | | |
| IA/0010 | IA_09_Deletion of manufacturing site | 04/03/2005 | n/a | | |

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| II/0008 | Update of Summary of Product Characteristics and Package Leaflet | 26/02/2004 | 25/03/2004 | SmPC, Annex II and PL | |
| I/0007 | 12_Minor change of manufacturing process of the active substance | 26/02/2003 | 11/03/2003 | | |
| I/0006 | 16_Change in the batch size of finished product | 26/02/2003 | 11/03/2003 | | |
| I/0005 | 15_Minor changes in manufacture of the medicinal product | 26/02/2003 | 11/03/2003 | | |
| I/0004 | 13_Batch size of active substance | 26/02/2003 | 11/03/2003 | | |
| I/0003 | 24_Change in test procedure of active substance | 26/02/2003 | 11/03/2003 | | |
| II/0001 | Extension of Indication | 18/10/2001 | 21/03/2002 | SmPC and PL | |
| I/0002 | 15_Minor changes in manufacture of the medicinal product<br>01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 04/07/2001 | n/a | | |