Paxlovid

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
IAIN/0053	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	13/03/2024		Annex II and PL	
PSUSA/10984 /202306	Periodic Safety Update EU Single assessment - nirmatrelvir / ritonavir	08/02/2024	n/a		PRAC Recommendation - maintenance

[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).

II/0049/G	This was an application for a group of variations. Grouped application comprising two type II variations (C.I.4) as follows: - Update of section 4.4 and 4.8 of the SmPC in order to clarify that toxic epidermal necrolysis has been reported with Paxlovid and to add toxic epidermal necrolysis to the list of adverse drug reactions (ADRs) with frequency Rare based on the cumulative review of MAH safety database and literature. - Update of section 4.4 and 4.8 of the SmPC in order to clarify that Stevens-Johnson syndrome has been reported with Paxlovid and to add Stevens-Johnson syndrome to the list of adverse drug reactions (ADRs) with frequency Rare, based on the cumulative review of MAH safety database and literature. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/12/2023		SmPC and PL	SmPC new text Sections 4.4 and 4.8 are updated to complement information regarding cutaneous adverse reactions. Thus, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) are included as they have been reported with Paxlovid use. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10984 /202212	Periodic Safety Update EU Single assessment - nirmatrelvir / ritonavir	14/09/2023	20/11/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10984/202212.

II/0040/G	This was an application for a group of variations. Grouped application comprising two type II variations as follows: - Update of section 4.3 of the SmPC in order to add more information for medicinal products such as finerenone ,naloxegol, lumacaftor/ivacaftor, etc, under medicinal products that are that are highly dependent on CYP3A for clearance or potent CYP3A inducer which ,therefore, could lead to serious and/or life-threatening reactions if co-administered with Paxlovid. - Update of section 4.5 of the SmPC in order to add drug-drug interaction information regarding co-administration of Paxlovid with different medicinal products that are metabolized by CYP3A4 or CYP2D6, transported by P-gp, or induce CYP3A4. 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	14/09/2023	26/10/2023	SmPC and PL	SmPC new text Sections 4.3 and 4.5 of the SmPC are updated to introduce additional information regarding drug-drug interaction with medicines that are metabolized by CYP3A4 or CYP2D6, transported by P-gp, or induce CYP3A4.Moreover, opportunity is taken to further adjust the drug- drug interaction recommendations. For more information, please refer to the Summary of Product Characteristics.
IB/0048	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/10/2023		SmPC and PL	
IB/0047	B.I.d.z - Stability of AS - Other variation	30/08/2023	n/a		

IA/0045	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	27/07/2023	n/a		
IA/0046/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/07/2023	n/a		
II/0043/G	This was an application for a group of variations. Grouped application comprising two type II variations as follows: -Update of section 5.1 of the SmPC in order to include new virology updates. - Update of sections 4.5 and 5.2 of the SmPC in order to update interaction information related to CYP2B6, MATE1 and OCT1. The RMP version 3.0 has also been submitted and updated. 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	20/07/2023	26/10/2023	SmPC	SmPC new text Within this variation new information about in vitro drug-drug interaction is included in the SmPC. This is: • CYB2B6 is added to the list of enzymes that may be induced by PAXLOVID and to the list of enzymes that nirmatrelvir does not inhibit. • MATE1 and OCT1 are added to the list of transporters for which nirmatrelvir has low potential to inhibit. The MAH has also updated the antiviral activity against SARS-CoV-2 variants. Overall, no decrease of antiviral activity of Paxlovid is expected against the currently circulating SARS-CoV-2 XBB.1.5 variant. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
II/0042	Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy, safety and pharmacokinetic information, based on updated results from studies C4671005 (EPIC-HR), C4671002 (EPIC-SR) and C4671006 (EPIC-PEP) as well as a supplemental report to Pop PK analysis PMAR-EQDD-C467a-DP4-1323, following the reanalysis of data after the removal of data related to four sites from the Paxlovid data analysis. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2023	26/10/2023	SmPC	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-42' For more information, please refer to the Summary of Product Characteristics.
IA/0044/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	28/06/2023	n/a		
II/0032	Update of section 4.4 of the SmPC in order to include	12/05/2023	23/06/2023	SmPC and PL	Hypertension was detected as a signal in post-marketing

	a warning on the risk of hypertension and to recommend a monitoring of blood pressure, and update of section 4.8 to add 'hypertension' to the list of adverse drug reactions (ADRs) with frequency 'uncommon', based on review of aggregate post-marketing data. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				experience. Post marketing analysis revealed at a least possible causal relationship to Paxlovid, in terms of temporal association and lack of confounding factors. A warning was consequently added in section 4.4 of the SmPC to further alert prescribers on the risk of hypertension and to recommend the monitoring of blood pressure during Paxlovid therapy (self-monitoring for outpatients) in order to initiate or re-assess antihypertensive treatment if necessary. For more information, please refer to the Summary of Product Characteristics.
II/0037	Submission of the updated population modeling analysis report (PMAR-EQDD-C467a-Other-1463): population pharmacokinetics of nirmatrelvir/ritonavir after oral administration in adults with/without COVID-19 - a pooled analysis of phase 1/2/3 data. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/05/2023	n/a		
II/0036	Update of sections 4.4, and 4.5 of the SmPC in order to include a warning related to Immunosuppressants and to update the information regarding co-administration with Immunosuppressants following the assessment of procedure II/0010/G based on the cumulative review of the spontaneous reports of over-exposure/over-toxicity of immunosuppressants and literature review. In addition, the MAH took this opportunity to introduce minor editorial changes to	30/03/2023	26/04/2023	SmPC	The Product Information has been updated to include a warning related to immunosuppressants, and to update the information regarding co-administration with immunosuppressants to enhance the physicians' attention on the complexity of the management in the target population. Such amendment follows the assessment of procedure II/0010/G based on the cumulative review of the spontaneous reports of over-exposure/over-toxicity of immunosuppressants and literature review.

	the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				For more information, please refer to the Summary of Product Characteristics and Package Leaflet
IA/0041/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/04/2023	n/a		
IB/0038	B.II.d.2.z - Change in test procedure for the finished product - Other variation	07/03/2023	n/a		
II/0019/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.e - Change in the specification parameters	26/01/2023	24/02/2023	Annex II	The SmPC section 5.1 has been updated by deleting the text below: "This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.z - Change in control of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				will be updated as necessary." The PL have been updated accordingly. The Annex II has been updated as follows: The three remaining specific obligations are deleted from the Annex II to the Opinion: 1. In order to improve the control strategy description and to confirm a consistent impurity profile, additional details should be included in the manufacturing process proposed for the active substance PF-07321332 for commercial supply. 2. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, the control strategy for the active substance PF-07321332 for the impurities including chiral impurities and the active substance should be fully established. 3. In order to ensure comprehensive control of impurities throughout the lifecycle of the product, full validation data for the HPLC method for assay and impurity testing, and for the residual solvent method used for the control of the active substance PF-07321332 should be provided
II/0026/G	This was an application for a group of variations. - Update of section 4.6 to update information related to the nonclinical data on developmental toxicity without change the recommendation based on cases reported on on-going clinical trials C4671002, C4671005 and C4671006, or reported during post-marketing, and the pre- and post-natal development study report 21GR149. - Update of section 5.1 of the SmPC in order	26/01/2023	15/02/2023	SmPC and PL	This grouped variation application concerns the several updates of the SmPC generated from different data sources. In relation to pregnancy, data on animal studies showed there were no nirmatrelvir-related severe manifestations of developmental toxicity at the highest dose tested in rats and rabbits. There were no nirmatrelvir-related adverse effects on pre- and post-natal development up to the highest dose tested in rats. Clinical data included identified 7 cases of maternal exposure during pregnancy in the on-

	to include final clinical efficacy and safety data based on the pivotal C4671005 study. Section 5.1 of the SmPC is also updated to include the antiviral activity of nirmatrelvir, against the sub-variants B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.4, and BA.5, antiretroviral resistance information based on in vitro assays and viral load rebound and treatment-emergent mutations observed in clinical practice. - Update of section 5.2 of the SmPC in order to update pharmacokinetic data on the effect of food on oral absorption following the submission of the results from studies C4671012, C4671013, C467104, C4671015 and C4671019. The first four studies are DDI studies conducted in healthy volunteers, with dabigatran, midazolam, carbamazepine and itraconazole, respectively. C4671019 was a phase 1, open-label, randomised, single dose, 2-sequence, 2-period crossover study to evaluate the effect of high-fat meal on the relative bioavailability of nirmatrelvir boosted with ritonavir following after single oral dose administration in healthy adult participants. The MAH has taken the opportunity to include editorial changes are included in sections 4.2, 4.5, 4.8 and 6.1 of the SmPC and the Package Leaflet. 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				going clinical trials: in 4 of the 7 cases, female study participants received placebo, in 3 of the 7 cases the pregnancies occurred in female partners of male study participants receiving nirmatrelvir/ritonavir. There were no associated adverse events in any of the 3 cases. In all 3 cases the outcome of the pregnancies was unknown at the time of reporting. At the time of reporting there were 2 post-marketing cases of pregnancy. In 1 of the post-marketing cases, a female took nirmatrelvir/ritonavir at 27 weeks gestation and adverse events of Ageusia and Anosmia were co-reported. In the second post-marketing case no adverse were reported. Based on review of available pregnancy data, no update to the recommendation is considered necessary, although based on this review section 4.6 of the SmPC is slightly updated. In relation to pharmacodynamic properties, in vitro cell culture data showed nirmatrelvir antiviral activity against Omicron subvariants BA.1, BA.2, BA.4 and BA.5 with EC50 fold changes compared to wild-type of ≤1. Also, a list of SARS-CoV-2 Mpro amino acid substitutions selected by nirmatrelvir in cell culture (with EC50 fold change >5) have been included in the SmPC, although the clinical significance of these mutations needs to be further understood. Lastly, in relation to antiviral rebound, the SmPC was updated to indicate that post-treatment viral nasal RNA rebounds were observed on Day 10 and/or Day 14 in a subset of Paxlovid and placebo recipients in EPIC-HR, irrespective of COVID-19 symptoms. The incidence of viral rebound in EPIC-HR occurred in both the Paxlovid treated participants and the untreated (placebo) participants, but at higher incidence in the Paxlovid arm (6.96% vs. 4.08%). So far, viral rebounds and symptoms

	new quality, preclinical, clinical or pharmacovigilance data				recurrences of COVID-19 are not associated with more severe disease or emergence of resistance. In relation to clinical efficacy, the first key secondary efficacy results from the pivotal trial C4671005 were updated. The observed event rate of COVID-19-related hospitalisation or death from any cause through Day 28 in the mITT1 analysis set who received treatment within 5 days of symptom onset was 66 of 1046 (6.310%) participants in the placebo group, and 9 of 1039 (0.866%) participants in the Paxlovid group, showing an 86.3% (72.6% to 93.1%) relative risk reduction in observed endpoint events. This change in the primary endpoint relative risk reduction from 87.8% as reported in the C4671005 primary completion date CSR was due to the reporting of a late event of a hospitalisation. This was a newly reported primary event (COVID-19-related hospitalization at Day 2) for a participant in the Paxlovid treatment group. For more information, please refer to the Summary of Product Characteristics.
II/0028/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	02/02/2023	n/a		

	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.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
IB/0033	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	24/01/2023	15/02/2023	SmPC, Labelling and PL	To update the product information to extend the shelf life of the finished product from '18 months' to '2 years' (section 6.3 of the SmPC) and to change the storage conditions from 'Do not store above 25 °C. Do not refrigerate or freeze.' to 'This medicinal product does not require any special storage conditions.'
PSUSA/10984 /202206	Periodic Safety Update EU Single assessment - nirmatrelvir / ritonavir	12/01/2023	n/a		PRAC Recommendation - maintenance

IB/0035	B.I.d.z - Stability of AS - Other variation	11/01/2023	n/a		
II/0010/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC to add hypersensitivity to the list of adverse drug reactions with frequency uncommon and anaphylaxis with frequency rare, including a warning on hypersensitivity reactions, based on a cumulative search of the MAH safety database. The Package Leaflet is updated accordingly. Update of section 4.5 of the SmPC in order to add drug-drug interaction information with dabigatran and rivaroxaban (P-gp substrate) based on the clinical study results from study C4671012, a pharmacokinetic study to estimate the effect of Paxlovid on the pharmacokinetics of dabigatran; the Package Leaflet is updated accordingly. Update of section 4.5 of the SmPC in order to update the drug-drug interaction information of midazolam based on the clinical study results from study C4671013, a pharmacokinetic study to estimate the effect of Paxlovid on the pharmacokinetics of midazolam. The MAH has taken the opportunity to update sections 4.3, 4.4 and 4.5 of the SmPC in relation to the drug-drug interaction profile for Paxlovid: pethidine has been removed as a contraindicated medication; tadalafil, silodosin, eplenerone, ivabradine, voclosporin, eletriptan, tolvaptan, and	15/12/2022	22/12/2022	SmPC and PL	Based on a safety review on the use of Paxlovid, the following changes are included in the product information: • Anaphylaxis and other hypersensitivity reactions have been reported with Paxlovid. Cases of Toxic Epidermal Necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of Paxlovid. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care. • Concomitant administration of Paxlovid is expected to increase dabigatran concentrations resulting in increased risk of bleeding. Reduce dose of dabigatran or avoid concomitant use. Refer to the dabigatran Summary of the product charactestics (SmPC) for further information. Rivaroxaban is not recommended as it's metabolisation may be impacted by the CYP3A4 inhibitory effect of Paxlovid but also its P-gp inhibitory effect. • The new information obtained from a drug-drug interaction study conducted with Paxlovid and midazolam does not downgrade the magnitude of interaction pertaining to inhibition of CYP3A4, although the pharmacokinetics information in the SmPC is updated accordingly. • Pethidine exposure is expected to decrease through the co-administration with Paxlovid due to the effect of ritonavir (as observed through the studies by Ramirez et al and Piscitelli et al). This indication will result in the increase

	apalutamide have been added as contraindicated medications; and sirolimus and lercanidipine have been added to list of interactions in section 4.5 of the SmPC. Also drugs propoxyphene, bepridil, encainide, astemizole, norbuprenophine, vorapaxar and desipramine have been removed from the SmPC as they are no longer marketed into the EU. Lastly, the SmPC was also updated to incite for a multidisciplinary approach for best handling the potential co-medications. The MAH is taking the opportunity to include editorial updates in sections 4.3, 4.4, 4.5, 5.1 and 5.2 of the SmPC. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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				of its metabolite known to be associated with opioid effects. Therefore it is recommended to monitor for respiratory depression and sedation. • Sildenafil and tadalafil regardless of their intended used, i.e. to treat erectile dysfunction or pulmonary arterial hypertension, are contraindicated. • Ritonavir as a pharmacokinetic enhancer inhibits CYP3A4 is expected to increase the plasma concentrations of immunosuppressants such as cyclosporine, everolimus, sirolimus and tacrolimus. This co-administration should only be considered with close and regular monitoring of immunosuppressant serum concentrations, to reduce the dose of the immunosuppressant so that to avoid over exposure and subsequent increase of serious adverse reactions of the immunosuppressant. It is important that the close and regular monitoring is performed during the co-administration with Paxlovid but also after the treatment with Paxlovid. • Additional contraindicated medication were added as a conservative approach: silodosin, eplenerone, ivabradine, voclosporin, eletriptan, tolvaptan, and apalutamide. • Propoxyphene, bepridil, encainide, astemizole, norbuprenophine, vorapaxar and desipramine have been removed from Paxlovid SmPC, as they are no longer approved drugs. • Lercanidipine should be avoided in co-administration with Paxlovid. The differential recommendation as compared to other calcium channel inhibitors as lercanidipine is particularly sensitive to CYP3A4 inhibition. • Depending on the type of drug-drug interaction, a

					multidisciplinary approach is recommended. For more information, please refer to the Summary of Product Characteristics.
IB/0034/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/12/2022	n/a		
IB/0029/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.z - Change in manufacture of the Finished Product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	01/12/2022	n/a		

R/0023	Renewal of the marketing authorisation.	10/11/2022	28/11/2022		
IAIN/0031/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code A.3 - Administrative change - Change in name of the AS or of an excipient	22/11/2022	22/12/2022	SmPC, Annex II, Labelling and PL	
II/0017	Submission of the final report from study in vivo efficacy of Pf-07321332 as a single agent or in combination with ritonavir in Balb/C Mouse-Adapted SARS-CoV-2 Model. The objective of this study was to evaluate whether Ritonavir has in vivo antiviral activity against SARS-CoV-2 and whether combination of Ritonavir with PF-07321332 increased the exposure of PF-07321332 in the mouse model and further decreased viral lung replication. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/11/2022	n/a		
II/0016/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to include the adverse drug reactions: nausea with frequency common, abdominal pain with frequency uncommon and malaise with frequency rare; based on the global safety database of the MAH and literature review. The Package Leaflet is updated accordingly.	13/10/2022	20/10/2022	SmPC and PL	

	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				
II/0007	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/09/2022	n/a		
IB/0022	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	19/09/2022	29/09/2022	SmPC	To change the summary of product characteristics, section 6.3 Shelf life from '1 year' to '18 months'.
IB/0020	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	15/09/2022	n/a		
II/0008	Submission of the final report from study PMAR-EQDD-C467a-DP4-1323, listed as a legally binding measure. This is the updated population pharmacokinetics module results including PK data from the patients enrolled in the EPIC-HR study of Paxlovid.	15/09/2022	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0025	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	09/09/2022	n/a		
IB/0027	B.I.b.z - Change in control of the AS - Other variation	08/09/2022	n/a		
II/0015	Submission of an exploratory lipid analysis conducted retrospectively using the left-over safety and PK samples from the multiple ascending dose (PART-2) of study C4671001 (phase I randomised controlled trial) submitted as part of the initial marketing authorisation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2022	n/a		
IB/0018	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	30/08/2022	29/09/2022	Annex II	To delete specific obligtion 4 in Annex II.
IA/0024	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 originally approved batch size	12/08/2022	n/a		

IA/0021	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	13/07/2022	n/a		
II/0012/G	This was an application for a group of variations. C.I.13 (type II): Submission of the whole body autoradiographic study report in rats with PF-07321332 (alone). C.I.13 (type II): Update of section 5.3 of the SmPC to indicate that no adverse effects were observed during the pre-and postnatal development study based on final study report for the pre- and postnatal development (21GR149). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/07/2022	29/09/2022	SmPC	
II/0009	Update of sections 4.3 and 4.5 of the SmPC in order to remove piroxicam as a contraindicated medicinal product and to indicate that piroxicam exposure may be decreased due to interaction with Paxlovid, based on scientific literature. The package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	23/06/2022	01/07/2022	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0006	B.II.e.z - Change in container closure system of the Finished Product - Other variation	14/06/2022	n/a		
IA/0014/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/05/2022	n/a		
IAIN/0013	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	18/05/2022	n/a		
IB/0005/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.z - Change in control of the AS - Other variation	11/05/2022	n/a		

	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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				
II/0003/G	This was an application for a group of variations. B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	22/04/2022	n/a		

II/0001/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.b.2.c.2 - Change to importer, batch release	22/04/2022	01/07/2022	PL	The Annex II has been updated to include the name and address of the new manufacturer responsible for batch release as follows: Pfizer Ireland Pharmaceuticals Little Connell Newbridge Ireland The PL have been updated accordingly.

	arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
II/0002	B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	17/03/2022	n/a		