Health Canada / Santé Canada

Health Products and Food Branch / Direction générale des produits de santé et des aliments

TERMS AND CONDITIONS
Company: Pfizer Canada ULC
Product: PAXLOVID (nirmatrelvir and ritonavir)
Dossier ID: HC6-024-e256440

Background:

The Food and Drug Regulations allows the Minister to impose or amend terms and conditions, and request additional information, in relation to a COVID-19 drug submission, Drug Identification Number (DIN), or establishment licence, at any time while it is in effect. In light of the severity of the COVID-19 pandemic, this allows the Minister to act quickly to gather important safety information or mitigate risk in a timely manner.

Depending on the requirement, terms and conditions can be ongoing (e.g., require a monthly report), have a defined time (e.g., a report is due to Health Canada on a specific day) or are to be completed once the data is available (e.g., a clinical trial is completed).

The status of the Terms and Conditions will be updated on a regular basis.

Status as of January 17, 2022:

Total Number: 29

Ongoing/pending: 29

Closed: 0

Table: Terms and Conditions

	Terms and Conditions	Issued	Status
1	Pfizer shall submit the final clinical study report (CSR) for the Phase 2/3 study EPIC-HR (study C4671005) to confirm the safety and efficacy of Paxlovid in the treatment of non-hospitalized adults with mild to moderate COVID-19 who are at risk of progressing to severe disease no later than January 31, 2022.	January 17, 2022	Expected by Jan 31, 2022
2	Pfizer shall submit the final viral sequencing results from participants enrolled in study C4671005 with complete data on the mutational pressure of nirmatrelvir on the SARS-CoV-2 3CL pro gene regions of interest no later than May 31, 2022.	January 17, 2022	Expected by May 31, 2022
3	Pfizer shall submit the full population PK (PopPK) report for Paxlovid, with the model being updated using all the data from the Phase 2/3 study EPIC-HR (study C4671005) no later than March 31, 2022. The PopPK analysis shall be updated to	January 17, 2022	Expected by March 31, 2022

	Terms and Conditions	Issued	Status
	provide a complete evaluation and description of nirmatrelvir PK in patients, and provide information about potential covariate effects including, but not limited to, the impact of age, sex, BMI, weight, race, ethnicity, hepatic impairment, and renal impairment.		
4	Pfizer shall submit the final (CSR) from a Phase 1, non-randomised, open-label study (Study C4671010) to assess the pharmacokinetics, safety and tolerability of nirmatrelvir boosted with ritonavir in adult participants with moderate hepatic impairment and healthy participants with normal hepatic function no later than September 30, 2022.	January 17, 2022	Expected by September 30, 2022
5	Pfizer shall submit the final CSR from a Phase 1, open-label, 3-treatment, 6-sequence, 3-period crossover study to estimate the effect of nirmatrelvir/ritonavir and ritonavir on the pharmacokinetics of midazolam in healthy participants (Study C4671013) no later than September 30, 2022.	January 17, 2022	Expected by September 30, 2022
6	Pfizer shall submit the final CSR from a Phase 1, open-label, 3-treatment, 6-sequence, 3-period cross-over study to estimate the effect of nirmatrelvir/ritonavir on the PK of dabigatran in healthy participants (Study C4671012) no later than September 30, 2022.	January 17, 2022	Expected by September 30, 2022
7	Pfizer shall submit the final CSR from a Phase 1, open-label, randomized, single dose, 2 sequence, 2 period crossover study to evaluate the effect of high-fat meal on the relative bioavailability of 300/100 PF-07321332/ritonavir final formulation in healthy participants (Study C4671019) no later than September 30, 2022.	January 17, 2022	Expected by September 30, 2022
8	Pfizer shall submit the final report from the ongoing rat pre- and postnatal development study (Study 00655272) no later than July 29, 2022.	January 17, 2022	Expected by July 29, 2022
9	Pfizer shall submit the final report from a 1-month oral gavage toxicity study of PF-07321332 in Wistar Han Rats with a 2-week recovery (Study 21GR122) no later than February 28, 2022.	January 17, 2022	Expected by February 28, 2022
10	Pfizer shall submit the final report from a 1-month BID oral gavage toxicity study of PF-07321332 in Cynomolgus Monkeys with a 2-week recovery (Study 21GR125) no later than February 28, 2022.	January 17, 2022	Expected by February 28, 2022
11	Pfizer shall submit the final report from an in vitro cell-based efficacy of nirmatrelvir against major SARS-CoV-2 variants (Study PF07321332_04Aug21_104040) no later than February 28, 2022.	January 17, 2022	Expected by February 28, 2022
12	Pfizer shall submit the final report from an in vitro qPCR-based efficacy of nirmatrelvir against major SARS-CoV-2 variants (Study PF-07321332_12Oct21_042713) no later than February 28, 2022.	January 17, 2022	Expected by February 28, 2022
13	Pfizer shall submit the final report from an in vitro evaluation of nirmatrelvir against reverse engineered recombinant SARS-CoV-2, characterizing viral fitness	January 17, 2022	Expected by

	Terms and Conditions	Issued	Status
	and resistance (Study PF-07321332_16Nov21_024518) no later than September 30, 2022.		September 30, 2022
14	Pfizer shall submit the report for a 24-week patient follow-up in study C4671005 no later than July 31, 2022.	January 17, 2022	Expected by July 31, 2022
15	Pfizer shall submit information on the manufacturing process and controls for nirmatrelvir for synthetic routes used at each one of the drug substance manufacturing sites included in section S2.1 in the Certified product Information Document (CPID) dated January 13, 2022, no later than July 29, 2022.	January 17, 2022	Expected by July 29, 2022
16	Pfizer shall submit an updated risk assessment on all potential impurities in the drug substance no later than July 29, 2022. This updated risk assessment shall take into consideration the additional information gained from process development to be provided in response to Ts&Cs #1, and from manufacturing additional lots of nirmatrelvir.	January 17, 2022	Expected by July 29, 2022
17	Pfizer shall submit the process validation protocol for the manufacture of nirmatrelvir tablets batches of commercial size no later than May 1, 2022.	January 17, 2022	Expected by May 01, 2022
18	Pfizer shall submit Canadian specific bilingual labelling for PAXLOVID™, no later than December 2, 2022 and implement such labelling once supplies are transitioned to Canadian dedicated supplies. Pfizer shall keep the Minister (i.e. Health Canada) informed of estimated timelines and proposed strategies concerning the development and implementation of Canadian-specific bilingual labels. a. During the period prior to implementation of the Canadian-specific bilingual labelling, Pfizer shall make the Canadian Product Monograph available to healthcare professionals.	January 17, 2022	Expected by December 02, 2022
19	Pfizer shall submit Monthly Summary Safety Reports (MSSR) for each of the first 6-months of marketing of nirmatrelvir/ritonavir in Canada, unless otherwise notified by Health Canada that it is not required. These MSSR shall be submitted at the end of the subsequent month; the first MSSR will have a data lock point of January 31, 2022 and shall be submitted February 28, 2022. These reports shall contain the following: a. Changes to reference safety information; b. Exposure data, stratified by country, age groups, race and ethnicity. Should specific demographic data not be available, Pfizer shall document this and provide an explanation in the MSSR; c. Number of adverse drug reactions (ADR) in Canada and Globally; d. Data in summary tabulations, both cumulative and interval. This will contain case reports (both serious and non-serious, medically confirmed and non-medically confirmed) received from post marketing authorization data sources, overall, and stratified by sex, country, age group and special populations (including pregnancy, breastfeeding, pediatrics, elderly, hepatic impaired, renal impaired,	January 17, 2022	Expected by February 28, 2022

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	cardiovascular impaired and immunocompromised patients), and summary tabulations of events by Preferred Term (PT) and System Organ Class (SOC) respectively for interval and cumulative periods [including a summary of relevant cases]. e. Review of special topics of interest including reports with a fatal outcome, reports concerning patients <18 years, elderly patients >75 years, pregnant and breastfeeding populations, drug interactions, off-label use and medication errors. f. Ongoing and closed signals in the interval from the MAH and other regulators; g. Discussion/assessment of data relevant to the safety concerns included in the Canadian Risk Management Plan (RMP) Addendum including any designated medical events (DMEs) [interval and cumulative]; and h. Risk/benefit considerations		
20	Pfizer shall provide an updated EU Risk Management Plan (RMP) and a Canadian Specific RMP Addendum following authorization, no later than February 7, 2022. This Canadian Specific RMP addendum must follow Health Canada guidance documents[1,2] and shall include the following: 1. Use in patients with renal impairment 2. Use in immunocompromised patients 3. Use in pregnancy and breastfeeding 4. Drug/antiviral resistance and treatment emergent mutations	January 17, 2022	Expected by February 07, 2022
21	Further terms and conditions are imposed on the Drug Identification Number **02524031** assigned to **PAXLOVID™ (nirmatrelvir; ritonavir)**. As these terms and conditions contain **Confidential Business Information (CBI)**, they are not made publicly available.	January 17, 2022	Pending availability of data

[1] Guidance on amendments to the Food and Drug Regulations for drugs for use in relation to COVID-19: Post-market requirements. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/food-drug-regulations-amendments-covid-19/post-market-requirements.html

[2] Guidance Document – Submission of Risk Management Plans and Follow-up Commitments. https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-submission-risk-management-plans-follow-commitments.html