BC COVID THERAPEUTICS COMMITTEE (CTC)
COVID THERAPY REVIEW and ADVISORY WORKING GROUP (CTRAWG)

Therapeutic Brief: Crushing Nirmatrelvir/ritonavir (Paxlovid™)

May 25, 2022

SUMMARY:

The monograph of nirmatrelvir/ritonavir states that the drug cannot be chewed or crushed and must be swallowed whole. The manufacturer stated that this is based on a lack of data to support alternative administration. Inability to crush nirmatrelvir/ritonavir has led to various negative consequences for BC patients, including delay of treatment. The CTC has conducted a review of the literature of pharmacokinetics and pharmacodynamics of nirmatrelvir/ritonavir, as well as other commonly used protease inhibitors and determined that nirmatrelvir/ritonavir are appropriate to be crushed. This decision was endorsed by CTRAWG and has been incorporated into the nirmatrelvir/ritonavir resources on the BCCDC website.

Recommendation: Nirmatrelvir and ritonavir, supplied as Paxlovid, can be split or crushed if the patient cannot swallow tablets, and made into a suspension for administration via feeding tubes (e.g., nasograstric, orogastric, gastrostomy and jejunostomy tubes).

Both ritonavir and nirmatrelvir can be spit or crushed and swallowed with apple sauce, pudding or any common food or liquid including dairy-containing products.

For feeding tubes, commercially available ritonavir powder for oral suspension or ritonavir solution can be used as per routine practices for other indications (e.g., HIV). If powder or solution are not available, ritonavir can be crushed and mixed with water to the desired consistency; the tube flushed with water after administration. Nirmatrelvir can be crushed and mixed with water to the desired consistency; the tube flushed with water after administration. Expert pharmacy or dietician consultation is recommended for smaller bore feeding tubes where obstruction is a concern (e.g., jejunal or naso-jejunal).

Due to lack of information pertaining to stability and storage of any nirmatrelvir suspension, it is recommended that any suspension made with crushed nirmatrelvir/ritonavir be extemporaneously compounded as single-dose preparation and not as multi-dose liquid.

This assessment and recommendation do not replace clinical judgement. Should crushing or administration of nirmatrelvir and ritonavir solutions be deemed inappropriate by the clinical team, alternatives for treatment of COVID-19 should be pursued.

BACKGROUND:

Ritonavir is a protease inhibitor supplied as a film-coated tablet, frequently used as part of HIV treatment. Despite advising against crushing ritonavir in its monograph, ritonavir is frequently crushed in clinical practice (e.g., for pediatric use). In addition, it comes supplied as a solution, power for oral suspension, and can also be compounded as a suspension; the first step of which is crushing the tablets. Various references support crushing ritonavir alongside other protease inhibitors used for HIV (e.g., darunavir), demonstrating adequate levels and virological response. The focus of this document is therefore nirmatrelvir.

Nirmatrelvir is a protease inhibitor supplied as a film-coated tablet that contains the following ingredients: Tablet core: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate; Film coat: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol and titanium dioxide. The tablet is not extended/delayed release and contains ingredients and coating commonly present in other medications, including other protease inhibitors.

In the monograph, it is stated that the nirmatrelvir and ritonavir tablets are to be swallowed whole. Two drug information requests submitted to the manufacturer were responded to, quoting lack of data to characterize pharmacokinetics and pharmacodynamics of nirmatrelvir/ritonavir as the rationale for the statement.

Meanwhile, questions regarding crushing of nirmatrelvir/ritonavir have been posed by nearly every health authority in BC and are frequently asked by patients accessing the CATe line. Such case-by-case assessments are handled by various pharmacists, CTC members and pharmacy leaders, and include a literature review and application of clinical judgement. In such cases, the benefits of crushing the drug have always been outweighed by the risk of crushing the tablets and crushing of nirmatrelvir/ritonavir already routinely occurs in practice when needed.

This document is intended to serve as a provincial reference approved by pharmacy leadership regarding the practice of crushing nirmatrelvir/ritonavir and will be updated regularly.

ASSESSMENT:

Nirmatrelvir is an intracellularly active protease inhibitor. After swallowing, it achieves peak concentrations of approximately 2210 ng/ml if ingested with ritonavir after 1-6 hours. In phase _I studies, oral administration was adequately characterized by a 2-compartment disposition model with first-order absorption.

Phase I studies of nirmatrelvir have evaluated doses of nirmatrelvir from 50mg to 2500mg given with or without ritonavir, *administered as a suspension*. When given as a suspension, nirmatrelvir 250mg and ritonavir 100mg suspension achieved maximum concentrations (Cmax) of approximately 2500 ng/ml (fasted) and 3000 ng/ml (fed) at 3 and 5 hours respectively (Tmax). These pharmacokinetics are essentially indistinguishable from the pharmacokinetics reported in the monograph of nirmatrelvir/ritonavir tablets: administration of nirmatrelvir 300mg tablets with ritonavir 100mg tablets had a mean Cmax of 2210 ng/ml (reported in µg/ml as 2.21 µg/ml) and a Tmax of 3.0 hours. Nirmatlervir suspension, especially if given on a full stomach, may produce slightly higher concentration of plasma nirmatrelvir compared to tablets. This is within the normal distribution range of the Cmax of nirmatrelvir tablets and not considered clinically relevant.

Nirmatlervir is highly protein bound (~70%); protein binding is not saturable and not affected by Cmax or Tmax.

Every protease inhibitor on the market used for HIV can be crushed, split, opened (if capsules) or comes supplied as a liquid formulation, either a suspension or solution. Protease inhibitors are intracellular drugs and plasma concentrations do not correlate well with their ability to inhibit intracellular proteases.

Various primary literature references, including systematic reviews, support alternative administration of protease inhibitors as suspensions or solutions. Detailed pharmacokinetic, pharmacodynamic and clinical outcomes supporting alternatives to tablets have been described. Various case reports and case series also support administration of these antiretrovirals via feeding tubes, including nasogastric, gastrostomy and jejunostomy tubes.

RECOMMENDATION:

Based on Phase I studies characterizing similar pharmacokinetics with nirimatlrevir/ritonavir suspension and various studies supporting crushing and alternative administration of protease inhibitors with similar pharmacokinetics and pharmacodynamics, the CTC sees no overwhelming contraindications to crushing, splitting or administering nirmatrelvir/ritonavir via feeding tubes. Due to a lack of data on compounding processes, stability and storage, it is recommended that any suspension be compounded fresh immediately before each dose.