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

Therapeutic Brief: Crushing Nirmatrelvir/ritonavir (Paxlovid™)

RECOMMENDATION SUMMARY:

Both ritonavir and nirmatrelvir (components of Paxlovid) ***can be split or crushed and mixed with apple sauce, pudding or any common food or liquid*** including dairy-containing products based on Phase I studies demonstrating that suspensions achieve similar pharmacokinetics to whole tablets.

Both ritonavir and nirmatrelvir be crushed and mixed with water to the desired consistency and considered for administration via feeding tubes; the tube should be flushed with water after administration. There are currently no precise recipes available; standard practices for administering regular powered tablets via feeding tubes should be applied. It may not be appropriate to administer crushed medications through smaller bore feeding tubes where obstruction is a concern (e.g., jejunal or naso-jejunal); consultation with an expert dietician or nursing staff may be required.

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

These recommendations 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.

The monograph of nirmatrelvir and ritonavir states that the drugs cannot be chewed or crushed and must be swallowed whole. The manufacturer remarks that this is based on a lack of data to support alternative administration. Inability to crush nirmatrelvir and ritonavir is associated delay of treatment or forgoing treatment in otherwise eligible patients. A review of the literature of the pharmacokinetics and pharmacodynamics of nirmatrelvir and ritonavir, as well as other commonly used protease inhibitors was conducted, which supports that crushing nirmatrelvir and ritonavir is reasonable and appropriate. Clinicians should use their judgement when recommending crushing nirmatrelvir/ritonavir and consult with an expert in cases of complex feeding needs (e.g., tubes).

BACKGROUND:

Ritonavir is a protease inhibitor supplied as a film-coated tablet, frequently used as part of HIV treatment. Despite advice 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 or power for

oral suspension (no longer available in Canada) and the crushed tablets can also be compounded as a suspension. 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 Practice Brief is therefore on 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 an extended/delayed release formulation and contains ingredients and a 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 and the responses quoted lack of data to characterize pharmacokinetics and pharmacodynamics of nirmatrelvir and ritonavir as the rationale for the statement for administration.

Meanwhile, questions regarding crushing of nirmatrelvir and ritonavir remain frequently asked by clinicians. Case-by-case assessments have been handled by various health care professionals through their review of the literature and judgement. In such cases, the benefits of crushing the drug have been determined to outweigh the risks, and so the crushing of nirmatrelvir and ritonavir has become routine in practice when needed.

DATA SUPPORTING CRUSHING NIRMATRELVIR:

Phase I studies of crushed nirmatrelvir have been carried out where nirmatrelvir was administered as an oral suspension at doses of 50 mg to 2500 mg given with or without ritonavir. Nirmatrelvir 250 mg and ritonavir 100 mg 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 of the nirmatrelvir oral suspension are essentially indistinguishable from the pharmacokinetics of the tablets reported in the monograph: administration of nirmatrelvir 300 mg 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 concentrations of plasma nirmatrelvir compared to tabletsThis is within the normal distribution range of the Cmax of nirmatrelvir tablets and not considered clinically relevant.

All protease inhibitors 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 with their mechanism of action. 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.