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PAXLOVID (nirmatrelvir tablets; ritonavir tablets) Administration via Enteral Feeding Tubes

Please see the Emergency Use Authorization (EUA) Fact Sheet for Healthcare Providers for PAXLOVID on important treatment considerations via the following link: https://labeling.pfizer.com/ShowLabeling.aspx?id=16474. In the event this link does not work, please access the product's approved Fact Sheet at www.pfizer.com. Note: select EUA Fact Sheet for Healthcare Providers is excerpted further in the document. This fact sheet is subject to potential changes and at any time the information excerpted below may not be the most current. Please always refer to the links above.

This letter regarding nirmatrelvir tablets; ritonavir tablets includes information for which the product is not authorized and/or inconsistent with the product uses described in the EUA Fact Sheet for Healthcare Providers. Pfizer does not suggest or recommend the use of in any manner other than as described in the EUA Fact Sheet for Healthcare Providers.

EMERGENCY USE AUTHORIZATION

Paxlovid has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death; and

The emergency use of Paxlovid is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb- 3(b)(1), unless the declaration is terminated or authorization revoked sooner.

SUMMARY

- Nirmatrelvir; ritonavir tablets should be swallowed whole and not chewed, broken or crushed, as no data is currently available.[1]
- Pfizer has not conducted any clinical studies designed specifically to evaluate the pharmacokinetics, safety, or efficacy of administering nirmatrelvir tablets; ritonavir tablets via enteral feeding tubes; therefore, Pfizer cannot recommend this method of administration. Any method of administration other than as described in the EUA Fact Sheet for Healthcare providers is inconsistent with the approved label.
- Both nirmatrelvir and ritonavir are immediate release film coated tablets, which is intended to enhance the ease of swallowing and the pharmaceutical elegance of the product.[2]
- Based on an internal laboratory study of physicochemical stability and compatibility, administration through nasogastric tube (NGT) may be accomplished via the preparation of a) a nirmatrelvir liquid suspension in a 20 mL syringe and of b) a separate ritonavir liquid suspension in a 20 mL syringe, followed by separate NGT administration of both suspensions. Both suspensions should be administered within 5 minutes of each other. The supplies and the protocol for dose preparation and administration via NGT are described in Table 1 and in Table 2.[3]
- Once the suspension preparation process has begun, all steps included in the protocol should be conducted in order and completed within a 4-hour period. To enable delivery of ritonavir within 5 minutes of dosing nirmatrelvir, both active doses' suspensions can be prepared prior to the initiation of the nirmatrelvir dosing.[3]
- The prepared suspensions were stable for up to 4 hours at room temperature when stored in the syringe. No chemical degradation was observed over the test period.[3]
- Specific pharmacokinetic studies have not formally evaluated the preparation method of the liquid suspensions followed by administration via NGT as described in this letter. Therefore, Pfizer cannot guarantee that the use of this method will result in comparable plasma concentrations as observed with oral administration of the intact nirmatrelvir; ritonavir film coated tablet formulations.

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SELECT FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR NIRMATRELVIR TABLETS; RITONAVIR TABLETS

Dosage and Administration

Dosage for Emergency Use of Paxlovid

Paxlovid is nirmatrelvir tablets co-packaged with ritonavir tablets.[1]

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect.[1]

Paxlovid (both nirmatrelvir and ritonavir tablets) can be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.[1]

Nirmatrelvir; ritonavir tablets should be swallowed whole and not chewed, broken or crushed, as no data is currently available.[1]

Pfizer has not conducted any clinical studies designed specifically to evaluate the pharmacokinetics, safety, or efficacy of administering nirmatrelvir tablets; ritonavir tablets via enteral feeding tubes; therefore, Pfizer cannot recommend this method of administration. Any method of administration other than as described in the EUA Fact Sheet for Healthcare Providers is inconsistent with the authorized label.

For further information regarding indications, dosage & administration, contraindications, warnings & precautions, interactions, and adverse effects, please refer to the full EUA Fact Sheet for Healthcare Providers.

LITERATURE SEARCH

As of September 27, 2022, a search of the published medical literature failed to identify any articles discussing the administration of nirmatrelvir tablets; ritonavir tablets (PF-07321332; ritonavir) via enteral feeding tubes, such us nasogastric tube (NGT), percutaneous endoscopic gastrostomy (PEG) tube, jejunostomy tube (J-tube), and orogastric tube. However, we are aware of unpublished internal information about the preparation of the nirmatrelvir; ritonavir for administration via NGT. A summary of this information follows.

The search is subject to the inherent limitations of database searching and cannot be considered exhaustive.

UNPUBLISHED INFORMATION

Background Information

Both nirmatrelvir and ritonavir are immediate release film coated tablets, which is intended to enhance the ease of swallowing and the pharmaceutical elegance of the product.[2]

Administration Via Nasogastric Tube (NGT)

Note that the unpublished data available below includes information of an off-label nature, and is based on a laboratory study of physicochemical stability and compatibility with the administration system (syringe and NGT); nirmatrelvir; ritonavir stored and administered outside the recommended conditions described in the Prescribing Information has not been tested or evaluated for pharmacokinetics, safety or efficacy.

Any method of administration other than those described in the EUA Fact Sheet for Healthcare Providers is considered off-label and done at the discretion of the healthcare professional.

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Pfizer has conducted a laboratory study to evaluate the physicochemical stability and compatibility of a) a liquid suspension containing 150 mg or 300 mg active dose of nirmatrelvir, prepared from 150 mg nirmatrelvir film coated oral tablets; b) a liquid suspension containing 100 mg active dose of ritonavir, prepared from 100 mg ritonavir film coated oral tablets. Both liquid suspensions, prepared separately, were prepared for administration via a syringe and NGT. The supplies required for dose preparation and administration via NGT are described in Table 1 and the protocol followed is described in Table 2. Once the suspension preparation process has begun, all steps of the protocol should be conducted in order and completed within a 4-hour period. Both suspensions should be administered within 5 minutes of each other.[3]

To enable delivery of ritonavir within 5 minutes of dosing nirmatrelvir, both active doses' suspensions can be prepared as described (see Table 2) in syringes prior to the initiation of the nirmatrelvir dosing. Once both nirmatrelvir and ritonavir doses have been prepared in the syringes, the nirmatrelvir suspension should be dosed and all described rinses performed. Immediately after completion of nirmatrelvir dose delivery, and within 5 minutes, the prepared ritonavir dose should be administered.[3]

The prepared suspensions were stable for up to 4 hours at room temperature when stored in the syringe. No chemical degradation was observed over the test period.[3]

All preparation was performed in a clean working space. During preparation, handlers were instructed to use appropriate personal protective equipment. Utilize local disposal and drug accountability procedures. Washing hands is recommended after handling.[3]

It is advised that only clinical site personnel or caregivers who are appropriately trained on the procedures detailed below may perform the preparation and administration procedures specified below.[3]

Table 1. Supplies for Preparation and Administration Via NGT[3]

The appropriate tablets of nirmatrelvir (one or two 150 mg tablets) and ritonavir (one 100mg tablet) for a single morning or evening dose.
Three latex-free, di(2-ethylhexyl)phthalate (DEHP) - free, and bisphenol A (BPA) - free polypropylene 20 mL syringes with a silicone gasket on the syringe plunger. 3 syringe tip caps.[4]
A cup of water (e.g. tap, bottled, sterile) at room temperature and an empty cup.
A pill crusher unit (e.g. Silent Knight®, Ocelco® or similar products).
A marking pen.
A NGT made of PVC, silicone, or polyurethane at sizes 8 FR or larger can be utilized with compatible syringes for dosing, due to potential for obstruction of the tubing with smaller diameter designs. NGT with either universal or ENFit connection designs are compatible with this procedure, including the use of an adaptor between universal and ENFit connections. Note: For NGT made of PVC, silicone, or polyurethane, weighted tip NGT have a high risk for clogging and should not be used.

Table 2. Protocol for Preparing a Dose of Nirmatrelvir Tablet(s); Ritonavir Tablet for NGT Administration*[3]

	Steps
1.	Label the syringes as "syringe 1" (for nirmatrelvir preparation), "syringe 2" (for NGT flushing and putting water in syringe 3) and "syringe 3" (for ritonavir preparation).
	Preparation of the Nirmatrelvir Tablet(s)
2.	Place the nirmatrelvir (pink) tablet(s) in "syringe 1" and replace plunger until it makes contact with the tablet(s), but being careful not to crush the tablet(s).
3.	Draw up water into "syringe 1" up to the 10 mL mark from the cup of room temperature water.
4.	Point "syringe 1" up and draw in air to the 15 mL mark. "Syringe 1" will now contain 10 mL water and the tablet(s) as well as 5 mL of air.
5.	Place a syringe tip cap on "syringe 1".
6.	Hold the barrel of "syringe 1" in fist with the thumb tightly over cap and shake vigorously up and down continuously for 15 seconds. If tablet(s) stick to the wall of the syringe, gently tap on clean surface to dislodge, and ensure contact with water.
7.	Lie "syringe 1" flat for a minimum of 3 minutes to allow the tablet(s) to **disintegrate**. Note: The consistency and color of the suspension should be milky and light pink, respectively.

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	Steps
8.	Use “syringe 2” to flush the NGT with 10 mL of water (with air removed) from the cup of room temperature water. Draw up water into “syringe 2” up to the 10 mL mark from the cup of room temperature water, place a syringe tip cap on “syringe 2” and set it aside to be used in Step 11.
9.	Shake “syringe 1” vigorously up and down again continuously for approx. 1 minute to ensure that the suspension is well mixed. (The tablet(s) should be completely disintegrated, leaving a milky and suspended solution.)
10.	Attach “syringe 1” to the NGT port. With the syringe tip angled upward (to avoid tube clogging), administer the contents of “syringe 1” to the NGT. Note: It is normal for a trace amount of material to remain inside ***Syringe 1***.
11.	Immediately following step 10, use “syringe 2” to flush the NGT with 10 mL of water (with air removed) from the cup of room temperature water prepared in Step 8.
12.	Draw up 10mL of water into “syringe 1” from the cup of room temperature water. Note: It is normal for a trace amount of the nirmatrelvir product to remain present in the cup of water after the tip has been immersed in the water.
13.	Point “syringe 1” up and draw in air to the 15 mL mark. “Syringe 1” will now contain 10 mL water and 5 mL of air. Place a syringe tip cap on “syringe 1”.
14.	Hold the barrel of “syringe 1” in fist with the thumb tightly over cap and shake vigorously up and down continuously for 15 seconds.
15.	Attach “syringe 1” to the NGT port. With the syringe tip angled upward, administer the contents of “syringe 1” to the NGT.
16.	Repeat steps **12-15** once more.
17.	Use “syringe 2” to flush the NGT with 10 mL of water (with air removed) from the cup of room temperature water.
	Preparation of the Ritonavir Tablet
18.	Remove the plunger from “syringe 3” and apply a syringe tip cap. Use “syringe 2” to fill “syringe 3” to the 5 mL mark from the cup of room temperature water. Place the open “syringe 3” containing the water in the empty cup.
19.	Gently **crush** an individual 100 mg ritonavir film coated tablet using a suitable pill crusher device to a fine powder. Note: If a plastic pouch is used, double bagging is recommended.
20.	Carefully transfer the powder into “syringe 3”.
21.	If the pill crusher device can be rinsed, use 5 mL of water from the cup of room temperature water using “syringe 2” to rinse the tablet residue from the pill crusher device into “syringe 3”. If the pill crusher device can’t be rinsed add an additional 5 mL of water from the cup of room temperature water using “syringe 2” to “syringe 3”.
22.	Carefully press the plunger into the syringe barrel, enough to secure the plunger in place. Point the syringe tip upward (away from people) and remove the syringe tip cap and press plunger to the 15 mL mark. “Syringe 3” will now contain 10 mL water and ritonavir powder, as well as 5 mL of air.
23.	Place a syringe tip cap on “syringe 3”.
24.	Hold the barrel of “syringe 3” in fist with the thumb tightly over cap and shake vigorously up and down continuously for 15 seconds.
25.	Lie “syringe 3” flat for a minimum of 3 minutes to allow further disintegration of the crushed ritonavir film coated tablet. Note: The consistency and color of the suspension should be milky and off-white, respectively.
26.	Draw up water into “syringe 2” up to the 10 mL mark from the cup of room temperature water, place a syringe tip cap on “syringe 2” and set it aside to be used in Step 29.
27.	Shake “syringe 3” vigorously up and down again continuously for approx. 1 minute to ensure that the suspension is well mixed.
28.	Attach “syringe 3” to the NGT port. With the syringe tip angled upward (to avoid tube clogging), administer the contents of “syringe 3” to the NGT. This step should be performed within 5 minutes of completion of step 17. Note: It is normal for a trace amount of material to remain inside “syringe 3”.
29.	Immediately following Step 28, use “syringe 2” to flush the NGT with 10 mL of water (with air removed) from the cup of room temperature water prepared in Step 26.
30.	Draw up 10 mL of water into “syringe 3” from the cup of room temperature water.

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	Note: It is normal for a trace amount of the ritonavir product to remain present in the cup after the tip has been immersed in the water.
31.	Point “syringe 3” up and draw in air to the 15 mL mark. “Syringe 3” will now contain 10 mL water and 5 mL of air. Place a syringe tip cap on “syringe 3”.
32.	Hold the barrel of “syringe 3” in fist with the thumb tightly over cap and shake vigorously up and down continuously for 15 seconds.
33.	Attach “syringe 3” to the NGT port. With the syringe tip angled upward, administer the contents of “syringe 3” to the NGT.
34.	Repeat steps **30-33** once more.
35.	Use “syringe 2” to flush the NGT with 10 mL of water (with air removed) from the cup of room temperature water. Replace NGT cap, clean all materials carefully and dispose of all consumables as directed by local site policy.

*Fasting Instructions: Please fast from all food-types for at least 2 hours before and 2 hours after administration of nirmatrelvir; ritonavir.

Administration with Other NGT Equipment or Via Other than NG Enteral Feeding Tubes

Pfizer does not have additional stability or compatibility information (e.g. with diluents other than water or with other equipment) to share other than what is described above. As such, Pfizer cannot comment about the use of equipment other than the one outlined above.

MANAGEMENT GUIDELINES

Pfizer can only support the use of nirmatrelvir tablets; ritonavir tablets as described within the EUA Fact Sheet for Healthcare Providers. Any use of nirmatrelvir tablets; ritonavir tablets outside of the EUA Fact Sheet for Healthcare Providers is considered “off-license” and done at the discretion of the healthcare professional.

Specific pharmacokinetic studies have not formally evaluated the preparation method of the liquid suspensions followed by administration via NGT as described in this letter. Therefore, Pfizer cannot guarantee that the use of this method will result in comparable plasma concentrations as observed with oral administration of the intact nirmatrelvir; ritonavir film coated tablet formulations.

REFERENCES

1 Paxlovid™ (nirmatrelvir tablets; ritonavir tablets) Emergency Use Authorization Fact Sheet for Healthcare Providers. Pfizer Inc.
2 PF-07321332; ritonavir Data On File 105 Pfizer.
3 PF-07321332; ritonavir Data On File 166 Pfizer.
4 PF-07321332; ritonavir Data On File 167 Pfizer.