ZANAMIVIR POWDER FOR INHALATION, PRE-METERED

(ZANAMIVIRI PULVIS PRO INHALATIONE)

- Draft proposal for inclusion for The International Pharmacopoeia
- 4 (July 2020)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidth@who.int) by **14 September 2020**.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.835:

ZANAMIVIR POWDER FOR INHALATION, PRE-METERED

(ZANAMIVIRI PULVIS PRO INHALATIONE)

Description	Date
Monograph drafted based on information received from manufacturers and on laboratory investigations.	February 2020
Discussion at the consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	May 2020
Draft monograph sent out for public consultation.	July – September 2020
Presentation to the 55 th WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2020
Further follow-up action as required	

[Note from the Secretariat. It is proposed to include the monograph on Zanamivir powder for inhalation, pre-metered in The International Pharmacopoeia. The monograph is based on a submission by a manufacturer and on laboratory investigations. It was developed in collaboration with the British Pharmacopoeia.]

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- **Category.** Antiviral, neuraminidase inhibitor.
- 59 **Labelling.** The designation of the container should indicate that the active ingredient is
- Zanamivir. The quantity of active ingredient is stated in terms of the equivalent amount
- of zanamivir per pre-metered unit.
- Additional information. Zanamivir inhalation powder is listed on the third invitation to
- 63 manufacturers of influenza-specific antiviral medicines to submit an Expression of
- Interest (EOI) for product evaluation to the WHO Prequalification Team: medicines.
- 65 **Labelling.** The label states the content of active ingredient per pre-metered unit.
- Manufacture. The fine-particle characteristics of the aerosol cloud generated by the
- powder for inhalation is controlled so that a consistent portion is deposited in the lung
- The test and limits for the aerodynamic assessment of the fine particles (fine particle
- 69 dose) should be agreed with the relevant regulatory authority.

Requirements

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- 71 Complies with the monograph on *Powders for Inhalation*.
- **Definition.** Zanamivir powder for inhalation, pre-metered consists of Zanamivir, in the
- form of microfine powder or equivalent, either alone or combined with a suitable carrier.
- 74 The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol. It
- 75 contains not less than 90.0% and not more than 110.0% of the amount of $C_{12}H_{20}N_4O_7$ per
- 76 pre-metered unit as stated on the label.

Identity tests

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- Transfer a quantity of the powder, nominally containing 10 mg of Zanamivir, into 78 A. a 50 mL flask, add 50 mL of a mixture of 1 volume of formamide R and 2 volumes 79 of methanol R and sonicate for five minutes to dissolve excipients. Filter the 80 suspension and dry the residue at 120 °C for about one hour. Carry out the test as 81 described under 1.7 Spectrophotometry in the infrared region. The infrared 82 absorption spectrum is concordant with the spectrum obtained from zanamivir RS 83 similarly treated. 84
 - B. Carry out test B.1 or, where a diode array detector is available, test B.2.
 - B.1 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to zanamivir in the chromatogram obtained with solution (2).
 - The absorption spectrum (1.6) of a solution of the powder in phosphate buffer, pH 7.5, TS, nominally containing 6 µg of Zanamivir per mL, when observed between 200 nm and 400 nm, exhibits a maximum at 260 nm.
 - B.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under "Assay". Record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and UV spectrum of the peak due to zanamivir in the chromatogram obtained with solution (2).
 - **Uniformity of delivered dose.** Complies with the test for Uniformity of delivered dose stated under *Powders for Inhalation* using the following method of analysis.
- 103 Carry out the test as described under *1.14.4 High-performance liquid chromatography*, 104 using the conditions given below under "Assay", with the following modifications.

- Prepare as a diluent a mixture of 60 volumes of acetonitrile R and 40 volumes of water
- 106 R.
- 107 Prepare the following solutions. For solution (1), dissolve the collected dose in
- sufficient diluent to produce a solution, nominally containing 0.05 mg of Zanamivir per
- mL. For solution (2), use solution (2) as described under "Assay".
- Inject alternately 10 μL of solutions (1) and (2).
- 111 Calculate the content of C₁₂H₂₀N₄O₇ in each delivered dose using the declared content
- of $C_{12}H_{20}N_4O_7$ in zanamivir RS.
- 113 **Related substances**. Carry out the test as described under 1.14.4 High-performance
- liquid chromatography, using the conditions given below under "Assay", with the
- 115 following modifications:
- Prepare the following solutions. For solution (1), transfer a quantity of the powder,
- nominally containing 20 mg of Zanamivir, into a 50.0 ml volumetric flask. Add
- about 45 mL of mobile phase and sonicate for five minutes. Allow to cool to room
- temperatures and make up to volume with mobile phase. For solution (2), dilute
- 1.0 mL of solution (1) to 200.0 mL with mobile phase. For solution (3), dissolve 5
- mg of zanamivir for system suitability RS (containing zanamivir and the impurities
- A, B, C and E) in mobile phase and dilute to 10 mL with the same solvent. For
- solution (4), dissolve 2.67 mg of zanamivir impurity F RS in mobile phase and
- dilute to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL
- with mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with mobile phase.
- For solution (5), dilute 1.0 mL of solution (2) to 200.0 mL with mobile phase.
- 127 Inject alternately 10 μL of solutions (1), (2), (3), (4) and (5) and record the
- chromatogram for 3 times the retention time of zanamivir.
- Use the chromatogram obtained with solution (3) and the chromatogram supplied
- with zanamivir for system suitability to identify the peaks due to the impurities A,

- B, C and E. Use the chromatogram obtained with solution (4) to identify the peak
- due to impurity F.
- The impurities are eluted, if present, at the following relative retention with
- reference to zanamivir (retention time about 9 minutes): impurity F about 0.30;
- impurity B about 0.60; impurity D about 0.71; impurity C about 0.77; impurity E
- about 0.83; impurity H about 1.14; impurity A about 2.75.
- The test is not valid unless, in the chromatogram obtained with solution (3), the peak-
- to-valley ratio (Hp/Hv) is at least 2.5, where Hp is the height above the baseline of the
- peak due to impurity E and Hv is the height above the baseline of the lowest point of
- the curve separating this peak from the peak due to impurity C. Also, the test is not
- valid unless in the chromatogram obtained with solution (5) the peak due to impurity F
- is obtained with a signal-to-noise ratio of at least 10.
- Measure the areas of the peaks corresponding to the impurities of zanamivir in the
- chromatograms obtained with solution (1) and (4) and the area of zanamivir in the
- chromatogram obtained with solution (2).
- Determine the percentage content of impurity F, considering the concentration of
- the impurity in solution (4) and the declared content of impurity F in zanamivir
- impurity F RS.
- The percentage content of impurity F is not greater than 0.01%.
- 150 For impurities other than impurity F, compare the peak areas of the impurities with
- the peak areas of zanamivir obtained with solution (2).
- In the chromatogram obtained with solution (1):
- the area of any peak corresponding to impurity A is not greater than the area
- of the peak due to zanamivir in the chromatogram obtained with solution (2)
- 155 (0.5%);

- the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.3 %);
- the area of any peaks corresponding to impurities C or D is not greater than 0.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.63, is not greater than 0.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %).
- The sum of the areas of all impurity peaks, including the corrected area of any peak corresponding to impurity E, is not greater than 2.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (1.2%).

 Disregard all peaks with an area or less than the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.1%).
- 170 **Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with cross-linked polyvinyl alcohol polymer with chemically bonded polyamine $(5 \mu m)^1$.
- As the mobile phase use a mixture of 60 volumes of acetonitrile R and 40 volumes of a 0.7 g/L solution of sulfuric acid (~1760 g/L) TS previously adjusted to pH 5.5 with ammonia (~1.7 g/L) TS.
- Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 234 nm. For identity test B.2 use a diode array detector in the range of 200 nm to 400 nm. Maintain the column temperature at 30 °C.
- Prepare as a diluent a mixture of 60 volumes of acetonitrile R and 40 volumes of water R.

¹ An Asahipak NH2P-50 column has been found suitable.

181	Prepare the following solutions. For solution (1), weigh and powder the contents of 24
182	pre-metered units. Transfer a quantity of the mixed contents, nominally equivalent to
183	50.0 mg of Zanamivir to a 100 mL volumetric flask. Add about 90 mL of water R and
184	sonicate for 5 minutes. Allow to cool to room temperature and make up to volume with
185	water R. Dilute 10.0 mL of this solution to 100.0 mL with diluent. For solution (2),
186	dissolve 50.0 mg of zanamivir RS in diluent and dilute to 100.0 mL with the some
187	solvent. Dilute 10.0 mL of this solution to 100.0 mL with diluent.
188	Inject alternately 10 μL each of solution (1) and (2). Record $$ the chromatogram for 3 $$
189	times the retention time of zanamivir.
190	Measure the areas of the peaks corresponding to zanamivir obtained in the
191	chromatograms of solution (1) and (2) and calculate the percentage content of
192	$C_{12}H_{20}N_4O_7 \ per \ pre-metered \ unit \ using \ the \ declared \ content \ of \ C_{12}H_{20}N_4O_7 \ in \ zanamivir$
193	RS.
194	Impurities
195	The impurities limited by the requirements of this monograph include those listed in
196	the monograph on Zanamivir.
150	the monograph on Zanamivii.
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198	Reference substances to be established
199	Zanamivir for peak identification RS (containing zanamivir and the impurities A,
200	B, C and E)
201	• It is intended to refer to the corresponding reference substance established
202	for the European Pharmacopoeia.

It is intended to refer to the corresponding reference substance established 204 by the European Pharmacopoeia. 205 Zanamivir RS 206 207 ICRS to be established. Reagent to be established 208 Ammonia (~1.7 g/L) TS 209 Ammonia (~17 g/L) TS, diluted to contain about 1.7 g of NH₃ per litre 210 (approximately 0.1 mol/L). 211 212