World Health Organization

ZANAMIVIR POWDER FOR INHALATION, PRE-METERED

(ZANAMIVIRI PULVIS PRO INHALATIONE)

Draft proposal for inclusion for *The International Pharmacopoeia*

(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**.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the "Current projects" link. If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

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 55th 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.*]*

ZANAMIVIR POWDER FOR INHALATION, PRE-METERED

(ZANAMIVIRI PULVIS PRO INHALATIONE)

Category. Antiviral, neuraminidase inhibitor.

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 manufacturers of influenza-specific antiviral medicines to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification Team: medicines.

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 dose) should be agreed with the relevant regulatory authority.

Requirements

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. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol. It contains not less than 90.0% and not more than 110.0% of the amount of $C_{12}H_{20}N_4O_7$ per pre-metered unit as stated on the label.

Identity tests

A. Transfer a quantity of the powder, nominally containing 10 mg of Zanamivir, into a 50 mL flask, add 50 mL of a mixture of 1 volume of formamide R and 2 volumes of methanol R and sonicate for five minutes to dissolve excipients. Filter the suspension and dry the residue at 120 °C for about one hour. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS similarly treated.

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.

Carry out the test as described under *1.14.4 High-performance liquid chromatography*, 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 R.

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).

Calculate the content of $C_{12}H_{20}N_4O_7$ in each delivered dose using the declared content of $C_{12}H_{20}N_4O_7$ in zanamivir RS.

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 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 .

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%.

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) (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%).

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 µm)*[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.

Prepare the following solutions. For solution (1), weigh and powder the contents of 24 pre-metered units. Transfer a quantity of the mixed contents, nominally equivalent to 50.0 mg of Zanamivir to a 100 mL volumetric flask. Add about 90 mL of water R and sonicate for 5 minutes. Allow to cool to room temperature and make up to volume with water R. Dilute 10.0 mL of this solution to 100.0 mL with diluent. For solution (2), dissolve 50.0 mg of zanamivir RS in diluent and dilute to 100.0 mL with the some solvent. Dilute 10.0 mL of this solution to 100.0 mL with diluent.

Inject alternately 10 µL each of solution (1) and (2). Record the chromatogram for 3 times the retention time of zanamivir.

Measure the areas of the peaks corresponding to zanamivir obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of $C_{12}H_{20}N_4O_7$ per pre-metered unit using the declared content of $C_{12}H_{20}N_4O_7$ in zanamivir RS.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Zanamivir.

Reference substances to be established

Zanamivir for peak identification RS (containing zanamivir and the impurities A, B, C and E)

- It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.

Zanamivir impurity F

- It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir RS

- ICRS to be established.

Reagent to be established

Ammonia (~1.7 g/L) TS

Ammonia (~17 g/L) TS, diluted to contain about 1.7 g of NH_3 per litre (approximately 0.1 mol/L).

***