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Zanamivir Inhalation Powder, pre-metered

General Notices

Zanamivir Inhalation Powder, pre-dispensed

Action and use

Neuraminidase inhibitor; treatment and prophylaxis of influenza.

DEFINITION

Zanamivir Inhalation Powder, pre-metered consists of Zanamivir Hydrate, in *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.

The inhalation powder, pre-metered complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of zanamivir, $C_{12}H_{20}N_4O_7$

92.0 to 108.0% of the stated amount.

IDENTIFICATION

A. Dissolve an amount of the inhalation powder in sufficient *water* to produce a solution containing the equivalent of 0.002% w/v of zanamivir. The light absorption, Appendix II B, of this solution in the range 200 to 320 nm exhibits a maximum at 234 nm.
B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the peak due to zanamivir in the chromatogram obtained with solution (2).

TESTS

Uniformity of delivered dose

Complies with the requirements stated under Inhalation Powders using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 40 volumes of *water* and 60 volumes of *acetonitrile*.

(1) Collect single doses of the preparation being examined using the procedure described under *Inhalation Powders*, *Uniformity of delivered dose* and dissolve the collected dose in sufficient solution A to produce a solution containing the equivalent of 0.005% w/v of zanamivir.
(2) 0.005% w/v of *zanamivir for assay EPCRS*.
(3) 0.005% w/v of *zanamivir for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *amino alkyl vinyl polymer for chromatography* (5 µm) (Asahipak NH2P-50 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 234 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

40 volumes of 0.005M *sulfuric acid*, adjusted to pH 6.2 with 50% v/v of *ammonia*, and 60 volumes of *acetonitrile*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* 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.

DETERMINATION OF CONTENT

Calculate the content of zanamivir, $C_{12}H_{20}N_4O_7$, per delivered dose from the chromatograms obtained and using the declared content of $C_{12}H_{20}N_4O_7$ in *zanamivir for assay EPCRS*. Repeat the procedure as described for pre-metered systems under *Inhalation Powders*, *Uniformity of delivered dose*.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Mix, with the aid of ultrasound, a quantity of the powder containing the equivalent of 10 mg of zanamivir with 20 mL of the mobile phase and dilute to 25 mL.
(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.
(3) 0.045% w/v of *zanamivir for system suitability EPCRS* in the mobile phase.
(4) 0.000004% w/v of *zanamivir impurity F EPCRS* in the mobile phase.
(5) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of delivered dose may be used. Allow the chromatography to proceed for 4 times the retention time of zanamivir.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to zanamivir (retention time about 9 minutes) are: impurity F, about 0.3; impurity B, about 0.6; impurity C, about 0.75; impurity E, about 0.8 and impurity A, about 2.9.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* 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.

LIMITS

Identify any peak corresponding to impurity E in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of the peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than the area of the principal peak 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 principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.01%);

the area of any *secondary peak* is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 2.4 times the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak, except for impurity F, with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A.

Solution A 40 volumes of *water* and 60 volumes of *acetonitrile*.

(1) Shake a quantity of the mixed contents of 20 pre-metered units containing the equivalent of 48 mg of zanamivir with 90 mL of *water*, mix with the aid of ultrasound, and add sufficient water to produce 100 mL. Dilute 1 volume to 10 volumes with solution A.
(2) 0.0048% w/v of *zanamivir for assay EPCRS*.
(3) 0.0045% w/v of *zanamivir for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of delivered dose may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* 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.

DETERMINATION OF CONTENT

Calculate the content of zanamivir, $C_{12}H_{20}N_4O_7$, in the inhalation powder from the chromatograms obtained and using the declared content of $C_{12}H_{20}N_4O_7$ in *zanamivir for assay EPCRS*.

LABELLING

The label states the content of active ingredient in terms of the equivalent metered dose. The quantity of active ingredient is stated in terms of the equivalent amount of zanamivir.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Zanamivir Hydrate.