DOLUTEGRAVIR TABLETS

DOLUTEGRAVIRI COMPRESSI

Draft proposal for inclusion in The International Pharmacopoeia

(September 2019)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (schmidt@who.int) by 31 October 2019.

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.

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Please send any request for permission to:

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/18.780:

**DOLUTEGRAVIR TABLETS**

**DOLUTEGRAVIRI COMPRESSI**

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First draft received from collaborating laboratory.</td>
<td>August 2018</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
<td>October 2018</td>
</tr>
<tr>
<td>Discussion at the Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.</td>
<td>2-3 May 2019</td>
</tr>
<tr>
<td>Draft monograph sent out for public consultation.</td>
<td>September – October 2019</td>
</tr>
<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations.</td>
<td>October 2019</td>
</tr>
<tr>
<td>Further follow-up action as required.</td>
<td></td>
</tr>
</tbody>
</table>

[Note from the Secretariat. The monograph on dolutegravir tablets is proposed for inclusion in The International Pharmacopoeia.]

Being the first public standard, the monograph is expected to play an important role in ensuring access to safe, effective and quality assured Dolutegravir tablets worldwide. Manufacturers of this product, regulatory authorities, procurement agencies and other stakeholders are therefore invited to provide their feedback to the Secretariat of The International Pharmacopoeia. If not already done, manufacturers are also invited to submit information and samples of their products. With their support manufacturers will help to ensure that the proposed monograph adequately controls the quality of the products they manufacture.

The World Health Organization (WHO) develops, establishes, and promotes international standards following the mandate given by WHO’s currently 194 Member States. WHO’s norms and standards are developed for adoption as legally binding national regulations and to serve as a basis for national standards and technical regulations. Besides, they play a prominent role for WHO Prequalification of medicine as well as UN/WHO procurement activities.

For information regarding the submission of specifications and samples, please contact Dr Herbert Schmidt at schmidt@who.int.
DOLUTEGRAVIR TABLETS

DOLUTEGRAVIRI COMPRESSI

Category. Antiretroviral (integrase inhibitor).

Storage. Dolutegravir tablets should be kept in a well-closed container.

Labelling. The designation of the container should state that the active ingredient is the sodium salt and the quantity should be indicated in terms of the equivalent amount of dolutegravir.


Requirements.

Comply with the monograph for Tablets.

Definition. Dolutegravir tablets contain Dolutegravir sodium. They contain not less than 90.0% and not more than 110.0% of the amount of dolutegravir (C₂₀H₁₉F₂N₃O₅) stated on the label.

Identity tests

Either test A or test B may be applied.

A. Carry out test A. 1, or where a diode array detector is available, test A.2.

A.1 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions and solutions 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 dolutegravir in the chromatogram obtained with solution (2).

To a quantity of the powdered tablets, nominally equivalent to 10 mg dolutegravir, add 40 mL methanol R, sonicate for five minutes, allow to cool to room
temperature, dilute to 50 mL and filter. Dilute 1 mL of the filtrate to 20 mL with methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 220 nm and 400 nm, exhibits maxima at about 258 nm and 321 nm.

A.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions and solutions given under “Assay”. Record the UV spectrum of the principle peak in the chromatograms with a diode array detector in the range of 220 and 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 the spectrum of the peak due to dolutegravir in the chromatogram obtained with solution (2).

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1 Carry out test as described under 1.14.1 Thin-layer chromatography using silica gel R6, or similar, as the coating substance and a mixture of 72 volumes of ethyl acetate R, 14 volumes of water R and 14 volumes of glacial acetic acid R as the mobile phase. Prepare as a solvent solution a mixture of 96 volumes of methanol R and 4 volumes of glacial acetic acid R. Apply separately to the plate 5 μL of each of the following two solutions. For solution (A), shake a quantity of the powdered tablets containing 10 mg of dolutegravir with 10 mL of the solvent solution and filter. For solution (B), use a solution containing 1 mg of dolutegravir sodium RS per mL solvent solution. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described above under text A.1 but using silica gel R5 as the coating substance. After drying the plate spray with basic potassium permanganate (5 g/L) TS. Examine the chromatogram in daylight.
The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

**Dissolution.** Carry out the test as described under 5.5 *Dissolution test for solid oral dosage forms* using as the dissolution medium 900 mL of a solution prepared by dissolving 2.5 g of sodium dodecyl sulfate R in 1000 mL dissolution buffer pH 6.8. Rotate the paddle at 50 revolutions per minute. At 20 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered solution to cool down to room temperature and dilute 5.0 mL of to 10.0 mL with dissolution medium. Use this solution as solution (1). For solution (2), dissolve a suitable amount of dolutegravir sodium RS in dissolution medium and dilute to a suitable volume with the same solvent.

Measure the absorbance as described under 1.6 *Spectrophotometry in the visible and ultraviolet regions* of a 1 cm layer of the resulting solutions at the maximum at about 258 nm, using the dissolution medium as the blank.

For each of the tablets tested, calculate the amount of dolutegravir (C$_{20}$H$_{19}$F$_2$N$_3$O$_5$) in the medium. Each mg of dolutegravir sodium is equivalent to 0.950 mg of dolutegravir.

Evaluate the results as described under 5.5 *Dissolution test for solid oral dosage forms*, Acceptance criteria. The amount of dolutegravir in solution for each tablet is not less than 80 (Q) of the amount declared on the label.

*[Note from the Secretariat. It is intended to determine the absorptivity value of dolutegravir during the establishment of dolutegravir sodium RS and to use this value for the calculation of the test result.]*

**Related substances.** Perform the test in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Carry out the test as described under 1.14.4 *High-performance liquid chromatography* using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded pentafluorophenyl groups (5 µm).¹

¹ A Kinetex F5 column or an Ascentis Express F5 column were found suitable.
Use the following conditions for gradient elution:

- mobile phase A: 0.186 g disodium edetate R in 1000 mL water R adjusted to pH 3.0 with phosphoric acid (~20 g/L) TS; and
- mobile phase B: 90 volumes of methanol R and 10 volumes of tetrahydrofuran R.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>60</td>
<td>40</td>
<td>Isocratic</td>
</tr>
<tr>
<td>1–30</td>
<td>60 to 50</td>
<td>40 to 50</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–40</td>
<td>50 to 30</td>
<td>50 to 70</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>40–55</td>
<td>30</td>
<td>70</td>
<td>Isocratic</td>
</tr>
<tr>
<td>55–57</td>
<td>30 to 60</td>
<td>70 to 40</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>57–65</td>
<td>60</td>
<td>40</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate at a flow rate of 0.8 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 258 nm. Maintain the column temperature at 25 °C.

Prepare the following solutions using as the diluent a mixture of 60 volumes of water R and 40 volumes of acetonitrile R.

For solution (1), transfer a quantity of the powdered tablets, nominally equivalent to 70.0 mg dolutegravir, to a 100 mL volumetric flask. Add about 70 mL diluent and sonicate for five minutes, cool to room temperature, dilute to volume and filter. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 10.0 mL of this solution to 50.0 mL. For solution (3), use a solution containing 0.5 mg of dolutegravir sodium for system suitability RS (containing dolutegravir sodium and impurity E) per mL. For solution (4), use a solution containing 1 mg of dolutegravir sodium for peak identification RS (containing dolutegravir sodium and the impurities A, B and D) per mL.

Inject alternately 10 µL of solutions (1), (2), (3) and (4).

Use the chromatogram obtained with solution (3) and the chromatogram supplied with dolutegravir sodium for system suitability RS to identify the peak due to the impurity E.
the chromatogram obtained with solution (4) and the chromatogram supplied with dolutegravir sodium for peak identification RS to identify the peak due to the impurity D.

The impurities, if present, are eluted at the following relative retentions with reference to dolutegravir (retention time about 27 minutes): impurity C about 0.65; impurity F about 0.72; impurity D about 0.77; impurities E about 0.86.

The test is not valid unless in the chromatogram obtained with solution (3) the resolution factor between the peaks due to impurity E and dolutegravir is at least 3. Also, the test is not valid unless in the chromatogram obtained with solution (2) the peak due to dolutegravir is obtained with a signal-to-noise ratio of at least 20.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than the area of the peak due to dolutegravir in the chromatogram obtained with solution (2) (0.2%).
- The sum of the areas of all impurity peaks is not greater than 5 time the area of the peak due to dolutegravir in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.5 times the area of the peak due to dolutegravir in the chromatogram obtained with solution (2) (0.1%).

**Assay.** Perform the test in subdued light and without any prolonged interruptions, preferably using low-actinic glassware. Carry out test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with pentafluorophenyl groups (5 µm).²

Use the following mobile phase: Dissolve 0.186 g of disodium edetate R in 1000 mL water R and adjust to pH 3.0 with phosphoric acid (~20g/L) TS. Mix 450 volumes of this solution with 550 volumes of methanol R.

Operate at a flow rate of 1.0 mL/minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 258 nm. For identity test A.2 use a diode array detector in the range of 220 nm to 400 nm. Maintain the column at a temperature of 30 °C.

² A Kinetex F5 column or an Ascentis Express F5 column were found suitable.
Prepare the following solutions using as the diluent a mixture of 60 volumes of water R and 40 volumes of acetonitrile R.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally equivalent to 100.0 mg of dolutegravir, to a 100 mL volumetric flask. Add about 70 mL of diluent and sonicate for five minutes, cool to room temperature and make up to volume with diluent. Filter and dilute 5.0 mL of the filtrate to 100.0 mL. For solution (2), dissolve 55.0 mg of dolutegravir sodium RS and dilute to 50.0 mL. Dilute 5.0 mL of this solution to 100.0 mL.

Inject alternately 20 µL each of solutions (1) and (2). Record the chromatogram for about 20 min.

Measure the areas of the peaks corresponding to dolutegravir obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of dolutegravir \((C_{20}H_{18}F_{2}N_{3}O_{5})\) in the tablets using the declared content of \(C_{20}H_{18}F_{2}N_{3}NaO_{5}\) in dolutegravir sodium RS. Each mg of dolutegravir sodium is equivalent to 0.950 mg of dolutegravir.

**Impurities.** The impurities limited by the requirements of this monograph include those listed in the monograph on Dolutegravir sodium, excluding impurity A and B.

**Reference substances invoked**

**Dolutegravir sodium RS.**

International Chemical Reference Substance (ICRS) to be established.

**Dolutegravir sodium for peak identification RS** (containing dolutegravir sodium and impurities A, B and D)

ICRS to be established.

**Dolutegravir sodium for system suitability RS** (containing dolutegravir sodium and impurity E)

ICRS to be established.