DACLATASVIR TABLETS

(DACLATASVIRI COMPRESSI)

Proposal for The International Pharmacopoeia

(January 2019)

DRAFT FOR COMMENT

Should you have any comments on this draft, please send these to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland; email: schmidt@who.int by 31 March 2019.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your email address (to jonessi@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

© World Health Organization 2019
All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of the World Health Organization. The draft should not be displayed on any website.

Please send any request for permission to:
Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Email: kopps@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.
**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/18.763:**

**Daclatasvir tablets**

*(Daclatasvirii comprimesi)*

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>First draft received from collaborating laboratory</td>
<td>March 2018</td>
</tr>
<tr>
<td>Discussion at the consultation on quality control laboratory tools and specifications for medicines</td>
<td>2–4 May 2018</td>
</tr>
<tr>
<td>Draft revision sent out for public consultation</td>
<td>June–July 2018</td>
</tr>
<tr>
<td>Preparation of Rev 1 considering the comments received during the public consultation</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>Revision 1 sent out for public consultation</td>
<td>February–March 2019</td>
</tr>
<tr>
<td>Discussion at the consultation on screening technologies and pharmacopoeial specifications for medicines</td>
<td>2-3 May 2019</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
</tr>
</tbody>
</table>

*Note from the Secretariat. The monograph on Daclatasvir tablets is proposed for inclusion in The International Pharmacopoeia.*

The methods and specifications were drafted based on information provided by manufacturers, found in the scientific literature and on laboratory investigations.

*Being the first public specification, this monograph is expected to play an important role in ensuring access to safe, effective and quality assured daclatasvir tablets worldwide. All manufacturers of these products are therefore invited to provide their feed-back to the Secretariat of The International Pharmacopoeia to help ensure that this proposed monograph adequately controls the daclatasvir tablets they manufacture.*
Daclatasvir tablets

(Daclatasviri compressi)

Category. Antiviral (Nonstructural protein 5A inhibitor)

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

Labelling. The designation of the container should state that the active ingredient is in the dihydrochloride form and the quantity should be indicated in terms of the equivalent amount of daclatasvir.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 30 mg and 60 mg daclatasvir.

Requirements

Comply with the monograph for Tablets.

Definition. Daclatasvir tablets contain Daclatasvir dihydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of daclatasvir (C₄₀H₅₀N₈O₆) 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 daclatasvir in the chromatogram obtained with solution (2).

To a quantity of powdered tablets, nominally equivalent to 10 mg daclatasvir, add 40 mL methanol R, sonicate for 5 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 230 nm and 400 nm, exhibits one maximum at 314 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 principal peak in the chromatograms with a diode array detector in the range of 230 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 the spectrum of the peak due to daclatasvir in the chromatogram obtained with solution (2).

B. 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 77 volumes of ethyl acetate R, 15 volumes of methanol R and 8 volumes of water R as the mobile phase. Apply separately to the plate 2 μL of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets, nominally equivalent to 50 mg of daclatasvir, with 5 mL of methanol R and filter. For solution (B) use a solution containing 11 mg of daclatasvir dihydrochloride RS per mL methanol R. 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 (365 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

Dip the plate in modified Dragendorff reagent TS. Dry it and 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 1000 mL of a solution prepared by dissolving 7.5 g of polyoxyethylene (23) lauryl ether R in 1000 ml dissolution buffer pH 6.8 TM. Rotate the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool down to room temperature.
If necessary, dilute a suitable volume of the filtrate with dissolution medium to obtain a solution containing 0.06 mg of daclatasvir per mL. Measure the absorbance as described under 1.6 Spectrophotometry in the visible and ultraviolet regions of a 1 cm layer of the resulting solution at the maximum at about 314 nm, using the dissolution medium as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of daclatasvir dihydrochloride RS in the dissolution buffer.

For each of the tablets tested calculate the amount of daclatasvir (C_{40}H_{50}N_{8}O_{6}) in the medium. Each mg of daclatasvir dihydrochloride is equivalent to 0.910 mg of daclatasvir.

Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria. The amount of daclatasvir in solution for each tablet is not less than 75\% (Q) of the amount declared on the label.

[Note from the Secretariat. It is intended to determine the absorptivity value of daclatasvir during the establishment of daclatasvir dihydrochloride RS. The value will then be included in the test description.]

Related substances. Carry out test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay” with the following modifications:

Use the following conditions for gradient elution:

- mobile phase A: 0.1\% (v/v) solution of trifluoroacetic acid;
- mobile phase B: mixture of 30 volumes of methanol R and 70 volumes of acetonitrile 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>80</td>
<td>20</td>
<td>Isocratic</td>
</tr>
<tr>
<td>1–25</td>
<td>80 to 55</td>
<td>20 to 45</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>25–30</td>
<td>55 to 30</td>
<td>45 to 70</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–35</td>
<td>30</td>
<td>70</td>
<td>Isocratic</td>
</tr>
<tr>
<td>35–37</td>
<td>30 to 80</td>
<td>70 to 20</td>
<td>Return to initial composition</td>
</tr>
</tbody>
</table>
Prepare the following solutions using as diluent a mixture of 80 volumes of mobile phase A and 20 volumes of mobile phase B.

For solution (1) transfer a quantity of the powdered tablets, nominally equivalent to 25.0 mg of daclatasvir, to a 50 mL volumetric flask. Add about 30 mL diluent and sonicate for 5 minutes, cool to room temperature and make up to the volume with the diluent and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL of this solution to 50.0 mL. For solution (3) use a solution containing 0.5 mg of daclatasvir for peak identification RS (containing daclatasvir and the impurities B, E, G, H, I and J) per mL.

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

The impurities, if present, are eluted at the following relative retentions with reference to daclatasvir (retention time about 17 minutes): impurity J about 0.21; impurity I about 0.62; impurity H about 0.76; impurities B and C about 1.12; impurity F about 1.16; impurities D and E about 1.22; impurity K about 1.39; impurity L about 1.66 and impurity G about 1.82.

Use the relative retentions and the chromatograms supplied with daclatasvir for peak identification RS and obtained with solution (3) to identify the peaks due to the impurities B, E, G, H, I and J in the chromatograms.

The test is not valid unless in the chromatogram obtained with solution (3) the peak-to-valley ratio (Hp/Hv) is at least 20, where Hp is the height above the extrapolated baseline of the peak due to the co-eluting impurities B and C and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to daclatasvir from the peak due to the co-eluting impurities B and C.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than 2 times the area of the peak due to daclatasvir in the chromatogram obtained with solution (2) (0.2%);
- the sum of all areas of all impurity peaks is not greater than 15 times the area of the peak due to daclatasvir obtained with solution (2) (1.5%). Disregard any peak with an
area less than the area of the peak due to daclatasvir obtained with solution (2) (0.1%).

Assay. 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 base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 μm). ¹

Use the following conditions for gradient elution:

<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>70</td>
<td>30</td>
<td>Isocratic</td>
</tr>
<tr>
<td>1 - 13</td>
<td>70 to 60</td>
<td>30 to 40</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>13–16</td>
<td>60 to 15</td>
<td>40 to 85</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>16–18</td>
<td>15</td>
<td>85</td>
<td>Isocratic</td>
</tr>
<tr>
<td>18–20</td>
<td>15 to 70</td>
<td>85 to 30</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>20–25</td>
<td>70</td>
<td>30</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate at a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. For identity test A.2 use a diode array detector in the range of 230 nm to 400 nm. Maintain the column temperature at 40 °C.

Prepare the following solutions using as diluent a mixture of 70 volumes of mobile phase A and 30 volumes of mobile phase B.

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally equivalent to 100.0 mg of daclatasvir, to a 100 mL volumetric flask. Add about 60

¹ A XBridge C18 column or a Zorbax SB C18 column were found suitable.
mL of diluent and sonicate for 5 minutes, cool to room temperature and make up to volume
with diluent. Filter and dilute 5.0 mL of the filtrate to 50.0 mL. For solution (2) dissolve 55.0
mg of daclatasvir dihydrochloride RS and dilute to 50.0 mL. Dilute 5.0 mL of this solution to
50.0 mL.

Inject alternately 20 µL each of solutions (1) and (2).

Measure the areas of the peak responses corresponding to daclatasvir obtained in the
chromatograms from solutions (1) and (2) and calculate the percentage content of daclatasvir
\((C_{40}H_{50}N_{8}O_{6})\) in the tablets using the declared content of \(C_{40}H_{50}N_{8}O_{6}\cdot2\text{HCl}\) in daclatasvir
dihydrochloride RS. Each mg of daclatasvir dihydrochloride is equivalent to 0.910 mg of
daclatasvir.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the
monograph on Daclatasvir dihydrochloride, excluding impurity A.

**Reagents to be added:**

Polyoxyethylene (23) lauryl ether R.

Synonym: Brij 35.

A commercially available reagent of suitable grade.

**Reference substances to be established:**

Daclatasvir dihydrochloride ICRS

Daclatasvir impurity A ICRS

Daclatasvir for peak identification ICRS (containing daclatasvir and the impurities B, E, G,
H, I and J)