



1 EFAVIRENZ (EFAVIRENZUM)

2 Draft proposal for revision in *The International Pharmacopoeia* 3 (June 2023)

4 DRAFT FOR COMMENT

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Sinéad Jones (jonesi@who.int, nsp@who.int).

Comments should be submitted through the online platform on or by **23 August 2023**. Please note that only comments received by this deadline will be considered for the preparation of this document.

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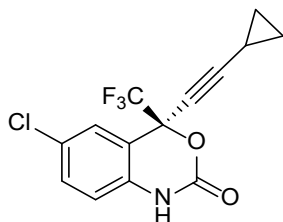
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**SCHEDULE FOR DRAFT PROPOSAL FOR REVISION IN THE
INTERNATIONAL PHARMACOPEIA
WORKING DOCUMENT QAS/23.928**

Description	Date
Draft proposal drafted.	February 2023 - May 2023
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications for Medicines.	April 2023
Draft proposal sent out for public consultation	June – July 2023
Further follow-up action as required.	

38 **Efavirenz (Efavirenzum)**



40 **Molecular formula.** C₁₄H₉ClF₃NO₂

41 **Relative molecular mass.** 315.7

42 **Chemical name.** (4*S*)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1,4-
43 dihydro-2*H*-3,1-benzoxazin-2-one; CAS Reg. No. 154598-52-4

44 **Description.** White to slightly pink powder.

45 **Solubility.** Practically insoluble in water R, freely soluble in methanol R.

46 **Category.** Antiretroviral (non-nucleoside reverse transcriptase inhibitor).

47 **Storage.** Efavirenz should be kept in a well-closed container, protected from light.

48 **Additional information.** Efavirenz may exhibit polymorphism.

49 **Requirements**

50 **Definition.** Efavirenz contains not less than 97.0% and not more than 102.0% of
51 C₁₄H₉ClF₃NO₂, calculated with reference to the dried substance.

52 **Identity test**

- 53 • Either tests A and F or tests B and F or any of two of tests C, D or E, together
54 with test F, may be applied

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS or with the *reference spectrum* of efavirenz.

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and efavirenz RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS.

B. Carry out the test as described under 1.14.1 Chromatography, High-performance liquid chromatography, using the conditions and solution (1) given under "Related substances, procedure 1". For solution (2), dissolve 12.5 mg efavirenz RS in 50.0 mL of a mixture of equal volumes of acetonitrile R and water R. Inject 35 µL each of solutions (1) and (2). Record the UV spectrum of the peaks due to efavirenz in the chromatograms with a diode array detector in the range of 210 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time and the UV spectrum of the peak due to efavirenz in the chromatogram obtained with solution (2).

C. Carry out the test as described under 1.14.1 Chromatography, High-performance liquid chromatography, using the conditions and solution (1) given under "Related substances, procedure 1". For solution (2), dissolve 12.5 mg efavirenz RS in 50.0 mL of a mixture of equal volumes of acetonitrile R and water R. Inject 35 µL each of solutions (1) and (2). The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to efavirenz in the chromatogram obtained with solution (2).

D. Carry out the test as described under 1.14.1 Chromatography, Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 µL of each of the two solutions in methanol R containing (A) 5 mg of the test substance per mL and (B) 5 mg of efavirenz RS per mL. After removing the plate from the chromatographic chamber, allow it to dry exhaustively 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 to that obtained with solution (B).

E. Prepare the test solution as described under "Assay". The absorption spectrum (1.6) of the final solution, when observed between 210 nm and 300 nm, exhibits a maximum at about 247 nm.

F. Carry out test E.1 or, where HPLC and the indicated chiral columns are available, test E.2.

F.1 Determine the specific optical rotation (1.4) of a 3 mg/mL solution in methanol R and calculate with reference to the dried substance; $[\alpha]_D^{20} = -89$ to -100 .

F.2 Carry out the test as described under 1.14.1 Chromatography, High-performance liquid chromatography, using the conditions and solution (1) given under "Impurity K (efavirenz enantiomer)". For solution (2), dissolve 10 mg efavirenz RS in 50.0 mL mobile phase. Inject 20 µL each of solutions (1) and (2). The retention time of the principal peak obtained with solution (1) corresponds to the retention time of the peak due to efavirenz in the chromatogram obtained with solution (2).

108 **Sulfated ash (2.3).** Use a platinum crucible, not more than 2.0 mg/g.

109 **Loss on drying.** Dry for 4 hours at 105 °C; it loses not more than 5 mg/g.

110 **Impurity K (efavirenz enantiomer).** Prepare fresh solutions and perform the tests
111 without delay. Protect solutions from light.

112 Carry out test as described under 1.14.1 Chromatography, High-performance liquid
113 chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with
114 particles of silica gel, the surface of which has been modified with chemically-bonded
115 amylose *tris* (3,5-dichlorophenyl carbamate) (5 µm)¹. As the mobile phase, use a
116 mixture of 980 volumes of hexane R, 20 volumes of ethanol R and 2 volumes of
117 diethylamine R.

118 Operate at a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet
119 spectrophotometer set at a wavelength of 252 nm. Maintain the column temperature at
120 25 °C.

121 Prepare the following solutions in mobile phase. For solution (1), dissolve 20 mg of
122 the test substance in 100.0 mL. For solution (2), dilute 1.0 mL of solution (1) to 100.0
123 mL. For solution (3), dilute 1.0 mL of this solution to 10.0 mL. For solution (4),
124 prepare a solution containing 0.1 mg of racemic efavirenz RS/ per mL.

125 Inject 20 µL each of solutions (1), (2), (3) and (4).

126 Use the chromatogram obtained with solution (4) to identify the peaks due to
127 efavirenz and impurity K. Impurity K is eluted with a relative retention of about 1.8
128 with reference to efavirenz (retention time about 9.3 minutes).

129 The test is not valid unless, in the chromatogram obtained with solution (4), the
130 resolution between the peaks due to efavirenz and impurity K is at least 9.0. Also, the

¹ A Lux Amylose-1 or Chiralpak AD column has been found suitable.

test is not valid unless, in the chromatogram obtained with solution (3), the peak due to efavirenz is detected with a signal-to-noise ratio of at least 10.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity K is not greater than 0.5 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.5%).

Related substances

Procedure 1. Prepare fresh solutions and perform the tests without delay. Protect solutions from light and use polypropylene HPLC vials to avoid possible degradation in certain types of glass vials.

Carry out the test as described under 1.14.1 Chromatography, 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 cyanopropyl groups (5 µm)².

Use the following conditions for gradient elution:

- mobile phase A: a mixture of methanol R, trifluoroacetic acid R and water R (1:0.005:9) (Note: use only freshly-opened trifluoroacetic acid – opened not longer than 6 months);
- mobile phase B: a mixture of methanol R, trifluoroacetic acid R and water R (9:0.005:1) (Note: use only freshly-opened trifluoroacetic acid – opened not longer than 6 months).

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–16	60 to 50	40 to 50	Linear gradient

² A Zorbax SB-CN column was found suitable.

16–23	50 to 35	50 to 65	Linear gradient
23–28	35 to 30	65 to 70	Linear gradient
28–29	30 to 20	70 to 80	Linear gradient
29–31	20	80	Isocratic
31–32	20 to 60	80 to 40	Return to initial composition
32–40	60	40	Re-equilibration

152 Prepare the following solutions in a mixture of equal volumes of acetonitrile R and
153 water R.

154 For solution (1), dissolve 25 mg of the test substance and dilute to 50.0 mL. Dilute
155 10.0 mL of this solution to 20.0 mL. For solution (2) dilute 1.0 mL of solution (1) to
156 100.0 mL. For solution (3), dilute 1.0 mL of solution (2) to 20.0 mL. For solution (4),
157 dissolve 1 mg of efavirenz impurity B RS in 10 mL. Dilute 1 mL of the resulting
158 solution to 25 mL. For solution (5), dissolve 1 mg of efavirenz RS in 10 mL of
159 solution (3). For solution (6) dissolve 10 mg of the test substance in 20 mL of a
160 mixture of equal volumes of methanol R and water R. Add 2 mL of sodium hydroxide
161 (~4 g/L) TS and heat in a stoppered vial at about 80 °C for 2 hours. Cool to room
162 temperature and dilute 1 mL of this solution to 10 mL with a mixture of equal
163 volumes of acetonitrile R and water R.

164 Operate at a flow rate of 1.5 mL per minute. As a detector, use an ultraviolet
165 spectrophotometer set at a wavelength of about 250 nm. Maintain the column
166 temperature at 40 °C.

167 Inject 35 µL each of solutions (1), (2), (3), (5) and (6).

168 Use the chromatogram obtained with solution (5) to identify the peak due to impurity
169 B and the chromatogram obtained with solution (6) to identify the peaks due to
170 impurity E, impurity F and impurity H.

The impurities, if present, are eluted at the following relative retentions with reference to efavirenz (retention time about 13 minutes): Impurity J about 0.19; impurity E about 0.53; impurity B about 0.93; impurity Q about 1.16; impurity R about 1.16; impurity S about 1.16; impurity C about 1.20; impurity G about 1.28; impurity H about 1.33, impurity F about 1.50; impurity L about 1.53; impurity M about 1.60; impurity N about 1.63; impurity D about 1.80, impurity A about 1.82, impurity I about 1.90; impurity O about 2.10; impurity P about 2.18.

The test is not valid unless, in the chromatogram obtained with solution (5), the resolution between the peaks due to impurity B and efavirenz is at least 1.2. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the peak due to efavirenz is obtained with a signal-to-noise ratio of at least 10.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B is not greater than 0.4 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.4 %);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.4, is not greater than 0.25 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.25 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor 3.8, is not greater than 0.15 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.15 %);
- the area of any peak corresponding to impurity I, when multiplied by a correction factor 1.8, is not greater than 0.15 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.15 %);
- the area of any peak corresponding to impurity C is not greater than 0.15 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.15 %);

- the area of any peak corresponding to impurity F, when multiplied by a correction factor 0.5, is not greater than 0.1 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.10 %);
- the area of any peak corresponding to impurity N, when multiplied by a correction factor 3.0, is not greater than 0.1 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.10 %);
- the area of any peak corresponding to impurity P, when multiplied by a correction factor 2.1, is not greater than 0.1 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.10 %);
- the area of any other impurity peak is not greater than 0.1 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.10%).
- The sum of the areas of all impurity peaks, including the corrected areas of any peaks corresponding to impurities D, E, I, F, N and P, is not greater than the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.05 times the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.05%).

Perform procedure 2 if the sum of the areas of the peaks corresponding to impurities Q, R and S, all with a relative retention of 1.16, is greater than the area of the peak due to efavirenz in the chromatogram obtained with solution (2) (0.10%).

Procedure 2 (impurities Q, R and S). Prepare fresh solutions and perform the tests without delay. Protect solutions from light.

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 particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm)³.

³ A Hypersil BDS C18 column or a Symmetry C18 column was found suitable.

225 Use the following conditions for gradient elution:

- 226 • mobile phase A: a mixture of acetonitrile R, trifluoroacetic acid R and water R
227 (55:0.05:45) (Note: use only freshly-opened trifluoroacetic acid – opened not
228 longer than 6 months);
- 229 • mobile phase B: a mixture of acetonitrile R, trifluoroacetic acid R and water R
230 (8:0.005:2) (Note: use only freshly-opened trifluoroacetic acid – opened not
231 longer than 6 months).

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–40	100 to 0	0 to 100	Linear gradient
40–45	0	100	Isocratic
45–46	0 to 100	100 to 0	Return to initial composition
46–50	100	0	Re-equilibration

232 Prepare the following solutions in mobile phase A.

233 For solution (1), dissolve 25 mg of the test substance and dilute to 50.0 mL. Dilute
234 10.0 mL of this solution to 20.0 mL. For solution (2), dilute 1.0 mL of solution (1) to
235 100.0 mL. For solution (3), dilute 1.0 mL of solution (1) to 20.0 mL .

236 Operate at a flow rate of 1.5 mL per minute. As a detector, use an ultraviolet
237 spectrophotometer set at a wavelength of about 250 nm. Maintain the column
238 temperature at 35 °C.

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

240 The test is not valid unless, in the chromatogram obtained with solution (3), the peak
241 due to efavirenz is obtained with a signal-to-noise ratio of at least 10.

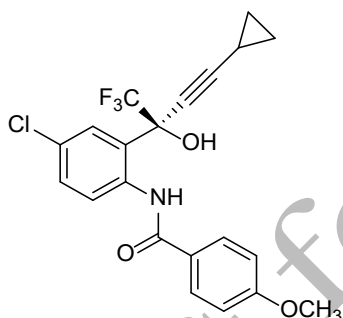
242 The impurities, if present, are eluted at the following relative retentions with reference
243 to efavirenz (retention time about 17 minutes): impurity Q about 1.10, impurity R
244 about 1.13 and impurity S about 1.14.

245 In the chromatogram obtained with solution (1):

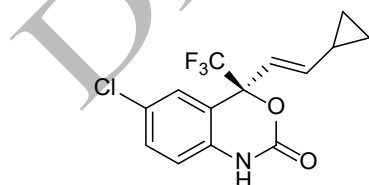
- 246 • the areas of any peaks corresponding to impurities Q, R or S are not greater
247 than 0.1 times the area of the principal peak in the chromatogram obtained with
248 solution (2) (0.10%).

249 **Assay.** Dissolve about 25.0 mg of the test substance in methanol R and dilute to 50.0
250 mL with the same solvent. Dilute 1.0 mL of this solution to 50.0 mL with the same
251 solvent. Measure the *absorbance* (1.6) of the resulting solution in a cuvette or cell
252 with an optical pathlength of 10 mm at the maximum at about 247 nm. Calculate the
253 amount of efavirenz ($C_{14}H_9ClF_3NO_2$) using an absorptivity value of 55.0 ($A_{1\%}^{1\text{cm}} =$
254 550).

255 **Impurities**

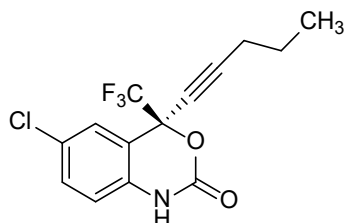


- 256
257 A. *N*-{4-Chloro-2-[(2*S*)-4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-2-
258 yl]phenyl}-4-methoxybenzamide (synthesis-related product);

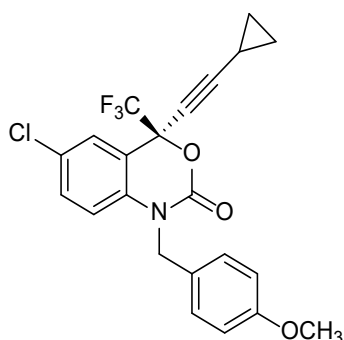


- 259
260 B. (4*S*)-6-Chloro-4-[(1*E*)-2-cyclopropyleth-1-en-1-yl]-4-(trifluoromethyl)-1,4-
261 dihydro-2*H*-3,1-benzoxazin-2-one; (*S,E*)-6-Chloro-4-(2-cyclopropylvinyl)-4-

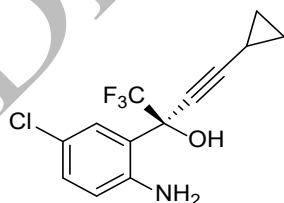
262 (trifluoromethyl)-2*H*-3,1-benzoxazin-2-one; efavirenz ethene analog,
263 (synthesis-related product);



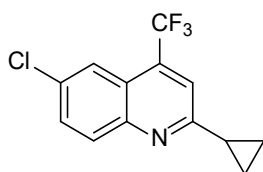
264
265 C. (4*S*)-6-Chloro-4-(pent-1-yn-1-yl)-4-(trifluoromethyl)-1,4-dihydro-2*H*-3,1-
266 benzoxazin-2-one; (*S*)-6-Chloro-4-(pent-1-ynyl)-4-(trifluoromethyl)-2*H*-3,1-
267 benzoxazin-2-one; efavirenz pentyne analog (synthesis-related product);



268
269 D. (4*S*)-6-Chloro-4-(2-cyclopropyleth-1-yn-1-yl)-1-[(4-methoxyphenyl)methyl]-4-
270 (trifluoromethyl)-1,4-dihydro-2*H*-3,1-benzoxazin-2-one; (*S*)-6-Chloro-4-
271 (cyclopropylethynyl)-1-(4-methoxybenzyl)-4-(trifluoromethyl)-2*H*-3,1-
272 benzoxazin-2-one; *N*-benzylefavirenz (synthesis-related product);

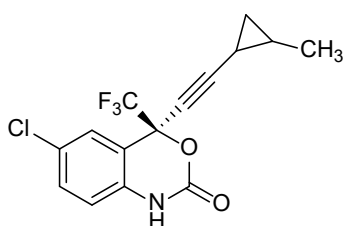


273
274 E. (2*S*)-2-(2-Amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol;
275 [(*S*)-2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol];
276 efavirenz amino alcohol (synthesis-related product and degradation product);



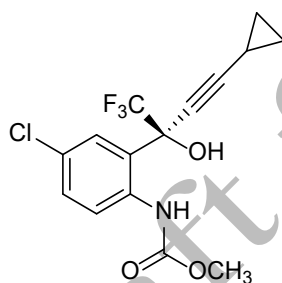
277

- 278 F. 6-Chloro-2-cyclopropyl-4-(trifluoromethyl)quinoline; quinoline analogue
279 (synthesis-related product and degradation product);



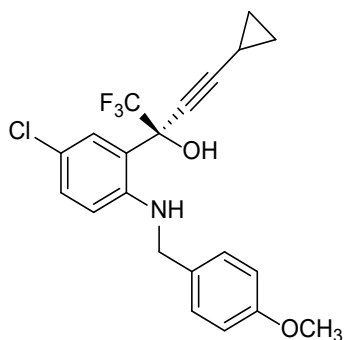
280

- 281 G. (4*S*)-6-Chloro-4-[2-(2-methylcyclopropyl)eth-1-yn-1-yl]-4-(trifluoromethyl)-
282 1,4-dihydro-2*H*-3,1-benzoxazin-2-one (mixture of four stereoisomers); (*S*)-6-
283 Chloro-4-{[(2*RS*,2*RS*)-2-methylcyclopropyl]ethynyl}-4-(trifluoromethyl)-2*H*-
284 3,1-benzoxazin-2-one; methyl efavirenz (synthesis-related product);



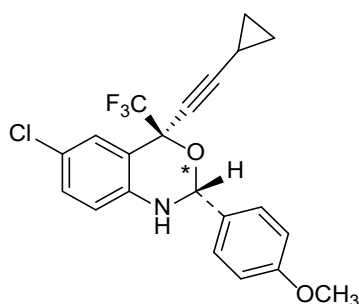
285

- 286 H. Methyl {4-chloro-2-[(2*S*)-4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-1-
287 yl]phenyl} carbamate; (*S*)-Methyl 4-chloro-2-(4-cyclopropyl-1,1,1-trifluoro-2-
288 hydroxybut-3-yn-2-yl)phenylcarbamate; efavirenz amino alcohol methyl
289 carbamate (synthesis-related product);



290

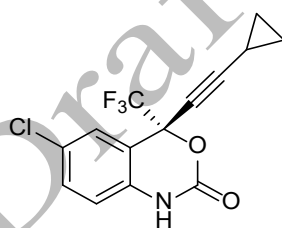
- 291 I. (2*S*)-2-(5-Chloro-2-[[4-methoxyphenyl)methyl]amino}phenyl)-4-cyclopropyl-
292 1,1,1-trifluorobut-3-yn-2-ol; *[(S)-N*-(4-Chloro-2-(4-cyclopropyl-1,1,1-trifluoro-
293 2-hydroxybut-3-yn-2-yl)phenyl)-4-methoxybenzamide; efavirenz
294 benzoylamino alcohol (synthesis-related product);



and epimer at C*

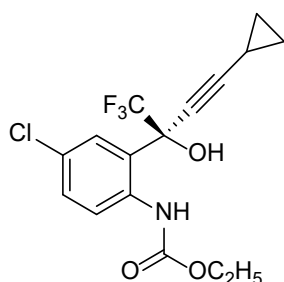
295

- 296 J. (2*RS*,4*S*)-6-Chloro-4-(2-cyclopropyleth-1-yn-1-yl)-2-(4-methoxyphenyl)-4-
297 (trifluoromethyl)-1,4-dihydro-2*H*-3,1-benzoxazine (synthesis-related product);



298

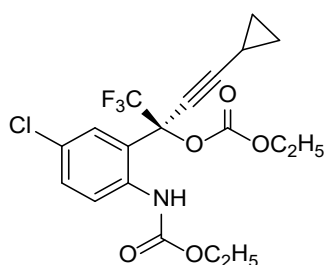
- 299 K. (4*R*)-6-Chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-2*H*-
300 3,1-benzoxazin-2-one (efavirenz enantiomer) (synthesis-related impurity);



301

302 L. (S)-Ethyl 4-chloro-2-(4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-2-yl)phenylcarbamate; efavirenz amino alcohol ethyl carbamate (synthesis-
303 related product);
304

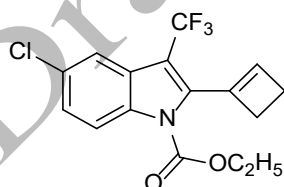
305 M. Unknown impurity;



306

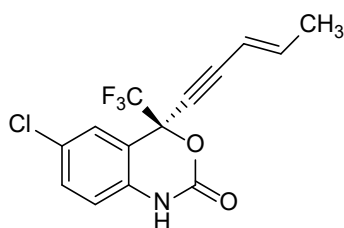
307 N. (S)-Ethyl 4-chloro-2-[4-cyclopropyl-2-(ethoxycarbonyloxy)-1,1,1-trifluorobut-
308 3-yn-2-yl]phenylcarbamate; efavirenz amino alcohol bis(ethoxycarbonyl)
309 (synthesis-related product);

310 O. Unknown impurity,



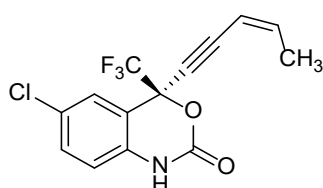
311

312 P. Ethyl 5-chloro-2-cyclobutenyl-3-(trifluoromethyl)-1H-indole-1-carboxylate;
313 cyclobutenylindole analogue (synthesis-related product);



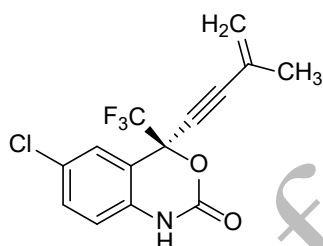
314

315 Q. (S,E)-6-Chloro-4-(pent-3-en-1-ynyl)-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-
316 one; efavirenz pent-3-ene-1-yne (*trans*) (synthesis-related product);



317

318 R. (S,Z)-6-Chloro-4-(pent-3-en-1-ynyl)-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-
319 one; efavirenz pent-3-ene-1-yne (*cis*) (synthesis-related product);



320

321 S. (S)-6-Chloro-4-(3-methylbut-3-en-1-ynyl)-4-(trifluoromethyl)-2H-3,1-
322 benzoxazin-2-one; efavirenz penteneyne (synthesis-related product).

323

324 **Reference substances described**

325 **Efavirenz RS**

326 ICRS already established.

327 **Efavirenz Impurity B**

328 ICRS already established.

329 **Efavirenz, racemic RS**

330 New ICRS to be established.

331

332

Draft for comments