

- 1 <\$Y> 3R1040TA
- 2 <\$1> **Ramipril Tablets**{ XE "Ramipril Tablets," }
- 3 <\$D> **Definition** Ramipril Tablets contain Ramipril.
- 4 <\$A2> *The tablets comply with the requirements stated under Tablets and with the*
5 *following requirements*
- 6 <\$A> **Content of ramipril, $C_{23}H_{32}N_2O_5$** 90.0 to 105.0% of the stated amount.
- 7 <\$A> **Identification**
- 8 <\$B> A Extract a quantity of the powdered tablets containing 10 mg of Ramipril
9 in 25 ml of 0.1M *hydrochloric acid*, centrifuge for 10 minutes and filter
10 through a 0.45- μ m filter. Evaporate the clear solution to dryness in an oven
11 at 40°. The *infrared absorption spectrum* of the residue, Appendix II A, is
12 concordant with the *reference spectrum* of ramipril (RS ..).
- 13 <\$A> B. In the Assay, the retention time of the principal peak in the
14 chromatogram obtained with solution (1) is the same as that of the principal
15 peak in the chromatogram obtained with solution (2).
- 16 <\$Y> *An infrared absorption reference spectrum will need to be prepared.*
- 17 <\$A> **Dissolution** Comply with the *dissolution test for tablets and capsules*,
18 Appendix XII D, using Apparatus II. Use as the medium 500 ml of 0.1M
19 *hydrochloric acid* and rotate the paddle at 75 revolutions per minute
20 Withdraw a sample of the medium and filter immediately through a 0.45-
21 μ m glass-fibre filter (Whatman GD/X is suitable), discarding the first 5 ml
22 of filtrate. Carry out the method for *liquid chromatography*, Appendix III D,
23 using the following solutions. For solution (1) use the filtered dissolution
24 medium diluted, if necessary, with 0.1M *hydrochloric acid* to produce a
25 solution expected to contain 0.0025 mg of Ramipril per ml. Solution (2)
26 contains 0.00025% w/v of *ramipril BPCRS* in 0.1M *hydrochloric acid*.
- 27 <\$C> The chromatographic procedure may be carried out using (a) a stainless
28 steel column (12.5 cm $\times$ 4.6 mm) packed with *octadecylsilyl silica gel for*
29 *chromatography* (5 μ m) (Nucleosil 100-C18 is suitable), (b) as the mobile
30 phase with a flow rate of 1.0 ml per minute a mixture, adjusted to pH 2.1
31 with *orthophosphoric acid*, of 420 volumes of *acetonitrile* and 580 volumes
32 of a solution containing 1.4% w/v *sodium perchlorate* and 0.58% w/v
33 *orthophosphoric acid* adjusted to pH 2.5 with *triethylamine* and (c) a
34 detection wavelength of 210 nm Inject 40 μ l of each solution.
- 35 <\$C> Calculate the total content of ramipril, $C_{23}H_{32}N_2O_5$, in the medium using the
36 declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.
- 37 <\$A> **Related substances** Carry out the method for *liquid chromatography*,
38 Appendix III D, using the following solutions For solution (1) mix with the

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aid of ultrasound for 10 minutes, and stirring, a quantity of the powdered tablets containing 25 mg of Ramipril with 50 ml of the mobile phase, centrifuge and use the clear solution. For solution (2) dilute 1 volume of solution (1) to 20 volumes with the mobile phase. For solution (3) dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Solution (4) contains 0.05% w/v of *ramipril BPCRS* and 0.0005% w/v of each of *ramipril impurity A EPCRS*, *ramipril impurity D EPCRS* and *ramipril impurity K BPCRS* in the mobile phase.

<S> The chromatographic procedure may be carried out using (a) a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-C18 is suitable), (b) as the mobile phase with a flow rate of 1.0 ml per minute a mixture, adjusted to pH 2.6 with *orthophosphoric acid*, of 350 volumes of *acetonitrile* and 680 volumes of a solution containing 1.4% w/v *sodium perchlorate* and 0.58% w/v *orthophosphoric acid* adjusted to pH 3.9 with *triethylamine* and (c) a detection wavelength of 210 nm. Inject 15 µl of each solution.

<S> When the chromatograms are recorded in the prescribed conditions, the retention time of ramipril is about 10 minutes and retention times relative to ramipril are about 0.6 for ramipril impurity K (diketopiperazine acid impurity), about 0.7 for ramipril impurity A (methyl ester impurity) and about 2.6 for ramipril impurity D (diketopiperazine impurity).

<A> The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to ramipril impurity K and ramipril impurity A is at least 1.0.

<S> In the chromatogram obtained with solution (1) the area of any peak corresponding to ramipril impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (5.0%), the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%), the area of not more than one such peak is greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (3) (0.2%) and the sum of the areas of all the *secondary peaks* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (6%).

<A> **Uniformity of content** Tablets containing less than 2.5 mg of Ramipril comply with the requirement stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. For solution (1) add 5 ml of 0.1M *hydrochloric acid* to one tablet, mix with the aid of ultrasound for 10 minutes, dilute, if necessary, with sufficient 0.1M *hydrochloric acid* to produce a solution containing 0.025% w/v of Ramipril and centrifuge. Solution (2) contains 0.025% w/v of *ramipril BPCRS* in 0.1M *hydrochloric acid*.

<S> The chromatographic procedure described under Dissolution may be used

- 1 <\$C> Calculate the content of $C_{23}H_{32}N_2O_5$ in each tablet using the declared
2 content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*
- 3 <\$A> **Assay**
- 4 <\$B> *For tablets containing 2.5 mg or more of Ramipril* Weigh and powder 20
5 tablets. Carry out the method for *liquid chromatography*, Appendix III D,
6 using the following solutions For solution (1) add 100 ml of 0.1M
7 *hydrochloric acid* to a quantity of powdered tablets containing 25 mg of
8 Ramipril, mix with the aid of ultrasound for 10 minutes and centrifuge.
9 Solution (2) contains 0.025% w/v of *ramipril BPCRS* in 0.1M *hydrochloric*
10 *acid*
- 11 <\$C> The chromatographic procedure described under Dissolution may be used.
- 12 <\$C> Calculate the content of $C_{23}H_{32}N_2O_5$ in the tablets using the declared content
13 of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*
- 14 <\$A> *For tablets containing less than 2.5 mg of Ramipril* Use the average of the
15 10 individual results obtained in the test for Uniformity of content
- 16 <\$Y> **Strengths available** Tablets containing 1.25, 2.5, 5 and 10 mg are available.
- 17 <\$Y> **New BPCRS**
18 Ramipril (Assay standard)
19 Ramipril impurity K (if available)
- 20 <\$Y> **New Infrared reference spectrum** Ramipril
- 21