Norgestimate and Ethinyl Estradiol Tablets

» Norgestimate and Ethinyl Estradiol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of norgestimate ($C_{23}H_{31}NO_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Ethinyl Estradiol RS. USP Norgestimate RS.*

Identification—The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Disintegration ⟨701⟩: 15 minutes.

Delete the following:

•**Dissolution** ⟨711⟩—[NOTE—Exercise care in filtering and handling solutions containing ethinyl estradiol to prevent adsorptive loss of the drug. Centrifugation may be used instead of filtration with nonadsorptive membrane filters. Withdraw dissolution aliquots with glass or polytef pipets or syringes that have been checked for adsorptive loss. Use glass dissolution vessels and polytef-coated or solid polytef paddles.]

Medium: 0.05% polysorbate 20; 600 mL.

Apparatus 2: 75 rpm.

Time: 20 minutes for Tablets labeled as containing 180 µg of $C_{23}H_{31}NO_3$ and 35 µg of $C_{20}H_{24}O_2$; 20 minutes for Tablets labeled as containing 215 µg of $C_{23}H_{31}NO_3$ and 35 µg of $C_{20}H_{24}O_2$; and 30 minutes for Tablets labeled as containing 250 µg of $C_{23}H_{31}NO_3$ and 35 µg of $C_{20}H_{24}O_2$.

Determine the amount of norgestimate ($C_{23}H_{31}NO_3$) and ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved by employing the following method.

Mobile phase—Prepare a degassed mixture of water and isopropyl alcohol (13 : 7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Norgestimate RS and USP Ethinyl Estradiol RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having known concentrations similar to those expected in the *Test solution*. [NOTE—A volume of methanol not exceeding 4% of the total volume of the *Standard solution* may be used to bring the standards into solution prior to dilution with *Medium.*]

Test solution—Use a filtered or centrifuged portion of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector (for norgestimate analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 234 nm and an emission wavelength of 304 nm, and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention times are about 7.5 minutes for ethinyl estradiol and 9.5 minutes for norgestimate; and the relative standard deviation for replicate injections is not more than 3.0% for the ethinyl estradiol and norgestimate peaks.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of each drug substance dissolved by the formula:

$$600C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of the appropriate analyte in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 80% *(Q)* of the labeled amounts of $C_{23}H_{31}NO_3$ and $C_{20}H_{24}O_2$ are dissolved in 20 minutes for Tablets labeled as containing 180 µg of $C_{23}H_{31}NO_3$ and 35 µg of $C_{20}H_{24}O_2$, and for Tablets labeled as containing 215 µg of $C_{23}H_{31}NO_3$ and 35 µg of $C_{20}H_{24}O_2$. Not less than 80% *(Q)* of the labeled amounts of $C_{23}H_{31}NO_3$ and $C_{20}H_{24}O_2$ are dissolved in 30 minutes for Tablets labeled as containing 250 µg of $C_{23}H_{31}NO_3$ and 35 µg of $C_{20}H_{24}O_2$.• (RB 1-Aug-2007)

Uniformity of dosage units ⟨905⟩: meet the requirements.

Change to read:

Chromatographic purity—

Mobile phase—Proceed as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a detector capable of detecting at •254 nm• (RB 1-Aug-2007) and a 4.6-mm × 5-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.5 for ethinyl estradiol, 1.0 for *(Z)*-norgestimate, and 1.2 for *(E)*-norgestimate; the resolution, *R,* between *(Z)*-norgestimate and *(E)*-norgestimate is not less than 1.5; and the relative standard deviation for replicate injections of the ethinyl estradiol and norgestimate peaks is not more than 2.0%.

Procedure—Inject a volume (about 50 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. •• (RB 1-Aug-2007) Calculate the percentage of any impurity having a relative retention time of about 0.2 or 0.4, relative to the *(Z)*-norgestimate peak, and detected at 254 nm in the portion of Tablets taken by the formula:

$$100(1.54)(C_Z / C_E)(r_i / r_Z)$$

in which 1.54 is the relative response factor of the impurity peaks; C_Z and C_E are the quantities, in mg, of *(Z)*-norgestimate and ethinyl estradiol, respectively, as determined in the *Assay;* r_i is the peak response for each impurity; and r_Z is the peak response for *(Z)*-norgestimate: the sum of the impurities having relative retention times of about 0.2 and 0.4 is not more than 4.0%.

Change to read:

Assay—

Mobile phase—Prepare a degassed mixture of water, tetrahydrofuran, and methanol (13 : 5 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve an accurately weighed quantity of dibutyl phthalate in methanol to obtain a solution having a concentration of about 0.05 mg per mL.

Standard preparation—•Dissolve accurately weighed quantities of USP Ethinyl Estradiol RS and USP Norgestimate RS in a volume of *Internal standard solution* equivalent to 80% of the final volume. Add a volume of water equivalent to 20% of the final volume, and mix to obtain a solution having a known concentration of about 7 µg per mL of ethinyl estradiol and a known concentration of

norgestimate similar to that expected in the *Assay preparation*. Mix, and pass through a filter having a porosity of 0.45 µm.•6

Assay preparation—•Add a number of Tablets, equivalent to 0.35 mg of ethinyl estradiol, to a suitable glass container, add 10 mL of water, and mix with a vortex mixer until the Tablets are completely disintegrated. Add 40 mL of *Internal standard solution*, and mix with a vortex mixer for at least 23 minutes. Sonicate the sample for at least 5 minutes, filter an aliquot through a suitable filter having a porosity of 0.45 µm, and use the filtrate.•6

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 5-cm column that contains 5-µm packing L1. The flow rate is about 2.1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for ethinyl estradiol, 1.0 for *(Z)*-norgestimate, 1.2 for *(E)*-norgestimate and 1.5 for dibutyl phthalate; the resolution, *R*, between *(Z)*-norgestimate and *(E)*-norgestimate is not less than 1.5; and the relative standard deviation of the peak response ratio of ethinyl estradiol, *(Z)*-norgestimate, and *(E)*-norgestimate to dibutyl phthalate for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ethinyl estradiol ($C_{20}H_{24}O_2$) in the portion of Tablets taken by the formula:

$$•50C(R_U / R_S)_{•6}$$

in which C is the concentration, in mg per mL, of USP Ethinyl Estradiol RS in the *Standard preparation;* and R_U and R_S are the ratios of the peak responses of ethinyl estradiol to dibutyl phthalate obtained from the *Assay preparation* and the *Standard preparation*, respectively. Calculate the quantity, in mg, of norgestimate ($C_{23}H_{31}NO_3$) in the portion of Tablets taken by the formula:

$$•50C[P_A(R_{UA} / R_{SA}) + P_S(R_{US} / R_{SS})]_{•6}$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard preparation;* P_A and P_S are the corresponding *(E)* and *(Z)* fractions of USP Norgestimate RS; R_{UA} and R_{SA} are the ratios of the peak responses of *(E)*-norgestimate to dibutyl phthalate obtained from the *Assay preparation* and the *Standard preparation*, respectively; and R_{US} and R_{SS} are the ratios of the peak responses of *(Z)*-norgestimate to dibutyl phthalate obtained from the *Assay preparation* and the *Standard preparation*, respectively.