Clotrimazole and Betamethasone Dipropionate Cream

» Clotrimazole and Betamethasone Dipropionate Cream contains not less than 90.0 per cent and not more than 110.0 per cent of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) and an amount of betamethasone dipropionate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the labeled amount of betamethasone ($C_{22}H_{29}FO_5$), in a suitable cream base.

Packaging and storage—Preserve in collapsible tubes or tight containers.

USP Reference standards ⟨11⟩**—**
USP Betamethasone Dipropionate RS
USP Clotrimazole RS
USP Clotrimazole Related Compound A RS
(*o*-Chlorophenyl)diphenylmethanol.
$C_{19}H_{15}ClO$ 294.78

Identification—The retention times of the major peaks for clotrimazole and betamethasone dipropionate in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay for clotrimazole and betamethasone and limit of clotrimazole related compound A.*

Microbial enumeration tests ⟨61⟩ **and Tests for specified microorganisms** ⟨62⟩**—**It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

Minimum fill ⟨755⟩**:** meets the requirements.

Assay for clotrimazole and betamethasone and limit of clotrimazole related compound A—

Dibasic ammonium phosphate solution—Dissolve 6.6 g of dibasic ammonium phosphate in water to make 1000 mL of solution.

Mobile phase—Prepare a mixture of methanol and *Dibasic ammonium phosphate solution* (7:3), and adjust with phosphoric acid to a pH of 7.0 ± 0.2. Pass through a membrane filter having a 0.45-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of progesterone in alcohol having a concentration of about 0.15 mg per mL.

Clotrimazole standard stock solution—Prepare a solution of USP Clotrimazole RS in alcohol having a known concentration of about 5 mg per mL.

Betamethasone dipropionate standard stock solution—Prepare a solution of USP Betamethasone Dipropionate RS in alcohol having a known concentration of about 6.4 *J* mg per mL, *J* being the ratio of the labeled amount, in mg, of betamethasone to the labeled amount, in mg, of clotrimazole in each g of Cream.

Clotrimazole related compound A standard stock solution—Prepare a solution of USP Clotrimazole Related Compound A RS in methanol having a known concentration of about 0.5 mg per mL.

Standard preparation—Transfer 1.0 mL of *Clotrimazole related compound A standard stock solution* to a suitable container, and evaporate to dryness in a water bath at room temperature under a stream of nitrogen. To the residue add 2.0 mL each of the *Clotrimazole standard stock solution, Betamethasone dipropionate standard stock solution,* and *Internal standard solution*, and mix.

Assay preparation—Accurately weigh a portion of Cream, equivalent to about 10 mg of clotrimazole, and transfer to a screwcapped, 50-mL centrifuge tube. Add 2.0 mL of *Internal standard solution* and 4.0 mL of alcohol, place the cap on the tube, and heat at 60 ° in a water bath for 10 minutes, with occasional shaking. Remove the tube from the bath, cool in an ice bath for 20 minutes, and promptly centrifuge. Transfer a portion of the supernatant to a test tube, and use this solution as the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 10- µm packing L1. The flow rate is about 1.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for betamethasone dipropionate, 1.2 for clotrimazole related compound A, 1.4 for progesterone, and 1.7 for clotrimazole; the resolution, *R,* between betamethasone dipropionate and clotrimazole related compound A is not less than 1.0, between clotrimazole related compound A and progesterone is not less than 1.5, and between progesterone and clotrimazole is not less than 1.8; and the relative standard deviation for replicate injections is not more than 2.0% determined from clotrimazole and betamethasone dipropionate, and not more than 4.0% determined from clotrimazole related compound A.

Procedure—Separately inject equal volumes (about 20 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 clotrimazole ($C_{22}H_{17}ClN_2$) in each g of Cream taken by the formula:

$$2(C/W)(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Clotrimazole RS in the *Clotrimazole standard stock solution; W* is the weight, in g, of Cream taken; and R_U and R_S are the peak response ratios of clotrimazole to progesterone obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the quantity, in mg, of betamethasone ($C_{22}H_{29}FO_5$) in each g of Cream taken by the formula:

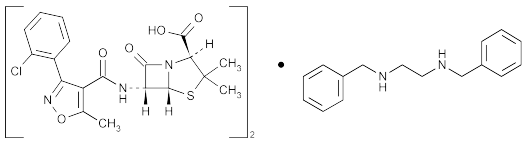
$$(392.46/504.60)(2)(C/W)(R_U / R_S)$$

in which 392.46 and 504.60 are the molecular weights of betamethasone and betamethasone dipropionate, respectively; *C* is the concentration, in mg per mL, of USP Betamethasone Dipropionate RS in the *Betamethasone dipropionate standard stock solution; W* is the weight, in g, of Cream taken; and R_U and R_S are the peak response ratios of betamethasone dipropionate to progesterone obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the quantity, in mg, of clotrimazole related compound A in each g of Cream taken by the formula:

$$(C/W)(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Clotrimazole Related Compound A RS in the *Clotrimazole related compound A standard stock solution; W* is the weight, in g, of Cream taken; and R_U and R_S are the peak response ratios of clotrimazole related compound A to progesterone obtained from the *Assay preparation* and the *Standard preparation,* respectively: the quantity of clotrimazole related compound A found is not more than 5.0% of the labeled quantity of clotrimazole in the Cream.

Cloxacillin Benzathine



$(C_{19}H_{18}ClN_3O_5S)_2 \cdot C_{16}H_{20}N_2$ 1112.11

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, [2*S*-(2α,5α,6*β*)]-, compd. with *N*,*N*′-bis(phenyl-methyl)-1,2-ethanediamine (2:1).

(2*S*,5*R*,6*R*)-6-[3-(*o*-Chlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid compound with *N*,*N*′-dibenzylethylenediamine (2:1) [23736-58-5].

» Cloxacillin Benzathine has a potency equivalent to not less than 704 µg and not more than 821 µg of cloxacillin ($C_{19}H_{18}ClN_3O_5S$) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to indicate that it is for veterinary use only. Where it is intended for use in preparing sterile dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of sterile dosage forms.

USP Reference standards ⟨11⟩**—**
USP Cloxacillin Benzathine RS
USP Cloxacillin Sodium RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solutions: Obtain the test solution as follows. To about 20 mg in a 50-mL conical flask, add 5 mL of 5 N sodium hydroxide, and heat on a steam bath for 20 minutes. Cool, transfer 1 mL of this solution to a separator containing 10 mL of 1.2 N sulfuric acid, and extract with 50 mL of ether. Wash the ether extract with 30 mL of water, and extract the ether layer with 50 mL of 0.1 N sodium hydroxide. Similarly prepare the Standard solution from about 15 mg of USP Cloxacillin Sodium RS.

Crystallinity ⟨695⟩: meets the requirements.

pH ⟨791⟩: between 3.0 and 6.5, in a suspension containing 10 mg per mL.

Sterility ⟨71⟩**—**Where the label states that Cloxacillin Benzathine is sterile, it meets the requirements when tested as directed for *Direct Inoculation of the Culture Medium* under *Test for Sterility of the Product to be Examined,* except to use Fluid Thioglycollate Medium containing polysorbate 80 solution (1 in 200) and an amount of sterile penicillinase sufficient to inactivate the cloxacillin in each tube, to use Soybean–Casein Digest Medium containing polysorbate 80 solution (1 in 200) and an amount of sterile penicillinase sufficient to inactivate the cloxacillin in each tube, and to shake the tubes once daily.

Water, *Method I* ⟨921⟩: not more than 5.0%.

Assay—

0.1 M Phosphate buffer—Dissolve 55.2 g of monobasic sodium phosphate in water, and dilute with water to 4 L.

Mobile phase—Combine 1000 mL of acetonitrile and 3000 mL of *0.1 M Phosphate buffer*. Adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 4.6 ± 0.2. Pass through a 0.45-µm nylon filter, and degas. [NOTE—The retention time of cloxacillin is very sensitive to the acetonitrile content of the *Mobile phase*.]

Diluent—Transfer 13.8 g of monobasic sodium phosphate to a 2-L volumetric flask, mix, and dilute with water to volume. Combine 1800 mL of the resulting solution with 1200 mL of acetonitrile. Adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 6.4.

Standard preparations—In duplicate, dissolve an accurately weighed quantity of USP Cloxacillin Sodium RS in *Diluent* to obtain solutions having known concentrations of about 112 µg per mL.

Assay preparations—In duplicate, dissolve an accurately weighed quantity of Cloxacillin Benzathine in *Diluent* to obtain solutions having concentrations of about 128 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 10- µm packing L1. The flow rate is about 1.5 mL per minute and the column temperature is 40°. Chromatograph the *Standard preparations,* and record the peak areas as directed for *Procedure:* the tailing factor is less than 2.0; the peak areas of the two *Standard preparations* agree within 98% to 102%; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparations* and the *Assay preparations* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{19}H_{18}ClN_3O_5S$ in each mg of Cloxacillin Benzathine taken by the formula:

$$P(C_S / C_U)(r_U / r_S)$$

in which P is the assigned potency, in µg of cloxacillin per mg, of USP Cloxacillin Sodium RS; C_S and C_U are the concentrations, in µg per mL, of cloxacillin sodium and cloxacillin benzathine in the *Standard preparations* and the *Assay preparations,* respectively; and r_U and r_S are the average peak areas of the cloxacillin peaks obtained from the *Assay preparations* and the *Standard preparations,* respectively.

Cloxacillin Benzathine Intramammary Infusion

» Cloxacillin Benzathine Intramammary Infusion is a suspension of Cloxacillin Benzathine in a suitable oil vehicle. It has a potency equivalent to not less than 90.0 per cent and not more than 120.0 percent of the labeled amount of cloxacillin ($C_{19}H_{18}ClN_3O_5S$).

Packaging and storage—Preserve in disposable syringes that are well-closed containers, except that where the Intramammary Infusion is labeled as sterile, the individual syringes or cartons are sealed and tamper-proof so that sterility is assured at time of use.

Labeling—Label it to indicate that it is for veterinary use only. Intramammary Infusion that is sterile may be so labeled.

USP Reference standards ⟨11⟩**—**
USP Cloxacillin Benzathine RS
USP Cloxacillin Sodium RS

Identification, *Infrared Absorption* ⟨197K⟩**—**Obtain the test specimen as follows. Transfer a quantity of Intramammary Infusion, equivalent to about 500 mg of cloxacillin, to a 50-mL centrifuge tube, add 25 mL of toluene, mix, and centrifuge. Decant and discard the toluene. Wash the residue with four 25-mL portions of toluene, sonicating for about 30 seconds after each addition of toluene. Dry the residue in vacuum over silica gel.

Sterility ⟨71⟩ (where labeled as being sterile)— It meets the requirements when tested as directed for *Direct Inoculation of the Culture Medium* under *Test for Sterility of the Product to be Examined,* except to use Fluid Thioglycollate Medium containing polysorbate 80 solution (1 in 200) and an amount of sterile