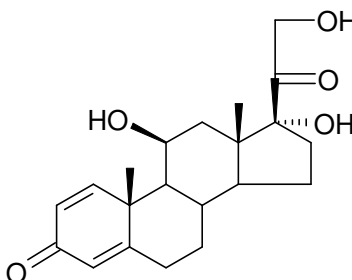


Prednisolone USP Anhydrous

Prednisolone USP Anhydrous Micronized



C₂₁H₂₈O₅

MW 360.45

NOMENCLATURE

Pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-, (11β)-

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione

CAS 50-24-8

Glucocorticoid

Laboratory Codes: PNU-5962, PNU-199999, SC-8189

USAN, INN, BAN, JAN: Prednisolone

DESCRIPTION

Prednisolone (anhydrous) from Pfizer is a white to practically white, odorless, crystalline powder. It melts at about 235°C, with some decomposition. It is very slightly soluble in water; soluble in methanol and in dioxane; sparingly soluble in acetone and in alcohol; slightly soluble in chloroform.

USP SPECIFICATIONS

| | <u>Test</u> | <u>Specification</u> |
|-------------------------------------|-------------|---------------------------------|
| Identification | | |
| A. Infrared | | Positive |
| B. Ultraviolet | | Positive |
| Absorptivity Difference Dried Basis | | Not More Than 2.5% |
| Specific Rotation (Dried Basis) | | +97° to +103° (dioxane) |
| Loss on Drying | | Not More Than 1.0% |
| Residue on Ignition | | Not More Than 0.5% (negligible) |
| Selenium | | Not More Than 0.003% |

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USP SPECIFICATIONS (continued)

| | <u>Test</u> | <u>Specification</u> |
|--|-------------|----------------------|
| Chromatographic Purity | | |
| Any Individual Impurity | | Not More Than 0.6% |
| Total Impurities | | Not More Than 2.0% |
| Assay (Dried Basis) | | 97.0% to 102.0% |
| Impurity Profile A (Prednisolone acetate) | | Not more than 0.3% |
| Impurity Profile B (Prednisone) | | Not More than 0.5% |
| Impurity Profile C ((Trienediol) | | Not More Than 0.6% |
| Impurity Profile D (20-hydroxy-21-aldehyde & hydrocortisone) | | Not More Than 0.4% |
| Impurity Profile E (20-hydroxy analog) | | Not More Than 0.6% |
| Impurities Unspecified | | Not More Than 0.1% |

In addition to the US Registration Specifications, the following apply to Prednisolone from Pfizer labeled “EP”.

CHARACTERS

Prednisolone (anhydrous) from Pfizer is a white or almost white, crystalline powder. It is hygroscopic. It is very slightly soluble in water; soluble in alcohol and in methanol, sparingly soluble in acetone, slightly soluble in methylene chloride. It melts at about 220°C.

Regarding the EP monograph statement that Prednisolone shows polymorphism, refer to the Pfizer “Polymorphism” statement.

EP SPECIFICATIONS

| | <u>Test</u> | <u>Specification</u> |
|---|-------------|-------------------------|
| Identification | | |
| A. Infrared | | Positive |
| B. Thin-layer Chromatography | | Positive |
| Specific Optical Rotation (Dried Basis) | | +96° to +102° (dioxane) |
| Related Substances | | Meets Test |
| Any Individual Impurity | | Not More Than 1.0% |
| Not More Than One Individual Impurity | | Not More Than 0.5% |
| Total Impurities | | Not More Than 2.0% |

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Loss on Drying
Assay (Dried Basis)

Not More Than 1.0%
97.0% to 103.0%

Additional Tests & Particle Size for Micronized Grades

| Parameter | Target | Method |
|----------------------|-------------------|---------------|
| Less Than 20 microns | Not Less Than 99% | Celloscope |
| Less Than 10 microns | Not Less Than 95% | Celloscope |
| Less Than 5 microns | Not Less Than 70% | Celloscope |
| Pathogens | Absence | Plate |
| Microcount Bacteria | NMT 1000 CFU/G | Plate |
| Microcount Fungi | NMT 500 CFU/G | Plate |

Regulatory Filings:

See Prednisolone under Regulatory

Organic Volatile Impurities

Of the solvents targeted in USP 26 General Chapter <467>, only methylene chloride may appear in bulk pharmaceutical products manufactured by Pfizer at the Kalamazoo plant. For those products where OVI testing is required, our material will meet the compendial limits for methylene chloride and other solvents that may be added to the target list in the future.

No OVI requirement exists in the USP 26 monograph for Prednisolone, but Prednisolone from Pfizer meets the requirements of USP 26 General Chapter <467>.

ICH Residual Solvents

As of 01 July 2000, Pfizer's laboratories began to internally report all solvents that are present above the assay detection limit. During the review of the batch data, it is verified that no solvents are present above the ICH limits. Therefore, all lots of Prednisolone released after 01 July 2000 will meet the ICH residual solvent guidance.

| <u>Solvent</u> | <u>Pfizer Specification *</u> | <u>ICH Class and Specification</u> |
|---------------------------|--------------------------------------|---|
| Residual Solvents (Total) | Not More Than 0.5% | |
| Acetone | Not More Than 5000 ppm | 3: Not More Than 0.5% |

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| | | | |
|---------------|------------------------|----|------------------------|
| Ethyl Acetate | Not More Than 5000 ppm | 3: | Not More Than 0.5% |
| Methanol | Not More Than 3000 ppm | 2: | Not More Than 3000 ppm |

* Pfizer does not have Registered Specifications for residual solvents, only quality control Targets.

ICH Residual Metals

Pfizer is currently developing a strategy to assess the detection and quantitation of ICH residual metals in Pfizer's active pharmaceutical ingredients. Currently, the only residual metals known to be present in Prednisolone from Pfizer are Selenium, with a US Registration Specification of NMT (not more than) 0.003%, and Osmium, with a quality control Target of NMT 10 ppm.

Chemical and TSE Certificate of Suitability

Certificate No. R0-CEP 1999-086-Rev 00 was granted to Pfizer by the European Directorate for the Quality of Medicines on 11 February 2002 for five years, for the product Prednisolone. A copy of the certificate is available upon request.

Viral Safety Statement for Active Pharmaceutical Ingredients (APIs)

Pfizer has reviewed the viral safety risks of its manufacturing practices for production of non-biological active pharmaceutical ingredients (APIs). The API Prednisolone presents no viral safety concerns. Pfizer APIs produced by bacterial or fungal fermentation and/or bioconversion processes are not considered to present viral safety risks. The raw materials used in the stages of production are sterilized prior to inoculation with a monoculture of the desired microorganisms. Only Pfizer's bioconversion reactions that employ purified enzymes (e.g. introduction of a double bond at the 1,2-position of the steroid ring system) use animal-derived materials that are not sterilized prior to introduction to the process. To support the safety of these enzymes, suppliers are required to provide documentation to Pfizer that these materials are in compliance with the CPMP and CVMP guidances on minimization of the risk of transmitting animal spongiform encephalopathy (TSE) agents via medicinal or veterinary products. Pfizer requires suppliers to provide similar certification for all TSE-risk animal-derived materials.

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Based upon the nature of our manufacturing processes and the control of animal-derived materials used in the manufacture of APIs, Pfizer is in compliance with applicable regulatory requirements for viral safety.

Statement Regarding Genetically Modified Materials in the Production of Active Pharmaceutical Ingredients (APIs)

The organism(s) currently used in the fermentation/bioconversion of plant sterols to produce intermediates that are chemically transformed into Prednisolone are not genetically engineered. However, Pfizer does not make any commitment that would preclude using genetically modified (recombinant) strains at some future date.

There are a number of ingredients used in the fermentation/bioconversion process that are derived from plants that are major agricultural products in the United States. It is well known that the U.S. agriculture industry has a growing reliance upon genetically modified (recombinant) plants such as corn and soybeans. Although some grain handlers and processors have contacted farmers about needing to segregate genetically modified seeds from non-genetically modified seeds, this concept has only recently been introduced and lacks effective enforcement and monitoring components. Pfizer has not evaluated the sources of ingredients for fermentation/bioconversion-derived intermediates and APIs relative to ingredients having been derived in part from genetically engineered varieties of plants or other organisms.

Vegetable Origin of Raw Materials

Pfizer produces steroid active pharmaceutical ingredients (APIs) by what is best described as a semi-synthetic process using a crude mixture of vegetable sterols that are isolated from various oilseeds as the starting material. These vegetable sterols, stigmasterol and sitosterol, are processed through several fermentation and chemical steps to yield Prednisolone.

Gluten

The raw materials used in the manufacture of Prednisolone are not derived from the gluten-containing grains wheat, rye, barley, or oats. Therefore, although Pfizer does not specifically assay for the presence of gluten, it is unlikely that any gluten proteins are present.

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Polymorphism

Evaluation of infrared (IR) spectra and x-ray diffraction (XRD) patterns indicate that Prednisolone from Pfizer has only one crystal structure (or crystal form). IR and XRD assays have been implemented to assure detection of any occurrence of undesired polymorphs.

Chirality

Prednisolone has seven chiral carbons: C8, C9, C10, C11, C13, C14, and C17. Pfizer's manufacturing process can modify the chirality of three of them: C9, C11, and C17.

Stereoisomer Content

Please note that none of the known impurities of Prednisolone are stereoisomers of Prednisolone. Therefore, the stereoisomer content is LT 0.1%.

Commercial Availability Of API And Impurities Standards

Hydrocortisone (PNU-1851, SC-3587)

EP Impurity A

EP (www.pheur.org), catalog # H1300000, 100 mg, €79

USP (www.usp.org), catalog # 1316004, 200 mg, \$150

Steraloids (www.steraloids.com), catalog # Q3880-000, 100 mg, \$8.50 (other sizes available)
(called "4-PREGNEN-11 β , 17, 21-TRIOL-3, 20-DIONE")

Research Plus (www.researchplus.com), catalog # 3312-16, 2 g and 10 g sizes (called "4-PREGNEN-11 β ,17 α ,21-TRIOL-3,20-DIONE (99.5%)")

Sigma, 9 catalog entries