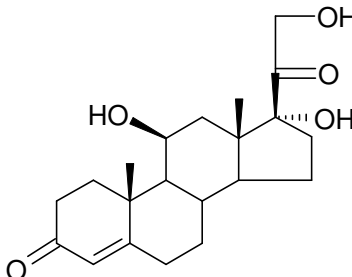


Hydrocortisone USP

Hydrocortisone USP Micronized



C₂₁H₃₀O₅

MW 362.46

NOMENCLATURE

Pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-, (11β)-
Cortisol

11β,17,21-Trihydroxypregn-4-ene-3,20-dione

CAS 50-23-7

Glucocorticoid

Laboratory Code: PNU-1851

USAN, INN, BAN, JAN: Hydrocortisone

DESCRIPTION

Hydrocortisone from Pfizer is a white to practically white, odorless, crystalline powder. It melts at about 215°C, with decomposition. It is very slightly soluble in water and in ether; 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)		+150° to +156° (dioxane)
Loss on Drying		Not More Than 1.0%
Residue on Ignition		Not More Than 0.5% (negligible)

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USP SPECIFICATIONS (continued)

<u>Test</u>	<u>Specification</u>
Chromatographic Purity	
Any Individual Impurity	Not More Than 0.5%
Total Impurities	Not More Than 2.0%
Organic Volatile Impurities	Meets Test
Assay (Dried Basis)	97.0% to 102.0%

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

CHARACTERS

Hydrocortisone from Pfizer is a white or almost white, crystalline powder. It is practically insoluble in water; sparingly soluble in acetone and in alcohol, slightly soluble in methylene chloride. It melts at about 220°C, with decomposition.

Regarding the EP monograph statement that Hydrocortisone 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)	+150° to +156° (dioxane)
Related Substances	Meets Test
Any Individual Impurity	Not More Than 0.5%
Total Impurities	Not More Than 1.5%
Loss on Drying	Not More Than 1.0%
Assay (Dried Basis)	97.0% to 103.0%

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

DESCRIPTION

Hydrocortisone from Pfizer is a white, crystalline powder. It is odorless. Its melting point is 212 - 220°C, with decomposition. It is sparingly soluble in methanol, in ethanol, and in dioxane; slightly soluble in chloroform; very slightly soluble in water and in ether.

JP SPECIFICATIONS

<u>Test</u>	<u>Specification</u>
Identification	

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3. Infrared	Positive
Optical Rotation (Dried Basis)	+150° to +156° (dioxane)
Purity Other Steroids	Meets Test
Loss on Drying	Not More Than 1.0%
Residue on Ignition	Not More Than 0.1%
Assay (Dried Basis)	97.0% to 102.0%

Additional Tests & Particle Size for Micronized Grades

Parameter	Target	Method
Less Than 20 microns	Not Less Than 80%	Celloscope
Particle size average	Not More than 15 microns	Celloscope
Particle size standard deviation	Report Results	Celloscope
Pathogens	Absence	Plate
Microcount Bacteria	NMT 500 CFU/G	Plate
Microcount Fungi	NMT 50 CFU/G	Plate

Regulatory Filings:

See Hydrocortisone 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.

Hydrocortisone 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 Hydrocortisone 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%	
Methanol	No individual specification	2: Not More Than 3000 ppm
Methylene Chloride	Not More Than 100 ppm	2: Not More Than 600 ppm

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* 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, no residual metals are known to be present in Hydrocortisone from Pfizer. However, a Chromium-containing raw material is used in the manufacturing process of an intermediate precursor to Hydrocortisone.

TSE Certificate of Suitability

Certificate No. R0-CEP 2000-354-Rev 00 was granted to Pfizer by the European Directorate for the Quality of Medicines on 24 October 2001 for five years, for the product Hydrocortisone. 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 Hydrocortisone 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.

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.

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

The organism(s) currently used in the fermentation/bioconversion of plant sterols to produce intermediates that are chemically transformed into Hydrocortisone are not genetically engineered.

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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 Hydrocortisone.

Gluten

The raw materials used in the manufacture of Hydrocortisone 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.

Polymorphism

Evaluation of infrared (IR) spectra and x-ray diffraction (XRD) patterns indicates that Hydrocortisone 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

Hydrocortisone 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 Hydrocortisone are stereoisomers of Hydrocortisone. Therefore, the stereoisomer content is LT 0.1%.

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Commercial Availability Of API And Impurities Standards

Hydrocortisone Acetate (PNU-2476, E-304)

EP Impurity C

- EP (www.pheur.org), catalog # H1400000, 100 mg, €79
- USP (www.usp.org), catalog # 1317007, 200 mg, \$150
- Steraloids (www.steraloids.com), catalog # Q3883-000, 100 mg, \$8.50 (other sizes available) (called “4-PREGNEN-11 β , 17, 21-TRIOL-3, 20-DIONE 21-ACETATE”)
- Research Plus (www.researchplus.com), catalog # 3313-16, 1 g and 5 g sizes (called “4-PREGNEN-11b,17a,21-TRIOL-3,20-DIONE 21-ACETATE”)
- Sigma, 5 catalog entries (called “Hydrocortisone 21-acetate”)

Hydrocortisone 21-Aldehyde (PNU-276847)

EP Impurity G

Call PCS for availability of standard, may require custom synthesis

Prednisolone (PNU-5962, PNU-199999, SC-8189, E-208)

EP Impurity A

- EP (www.pheur.org), catalog # P2700000, 200 mg, €79
- USP (www.usp.org), catalog # 1555005, 200 mg, \$150
- Steraloids (www.steraloids.com), catalog # P0650-000, 100 mg, \$5 (other sizes available) (called “1, 4-PREGNADIEN-11 β , 17, 21-TRIOL-3, 20-DIONE”)
- Research Plus (www.researchplus.com), catalog # 3010-16, 1 g and 5 g sizes (called “1,4-PREGNADIEN-11b,17a,21-TRIOL-3,20-DIONE”)
- Sigma, 4 catalog entries

Cortisone (PNU-3365, PNU-199621, PNU-199982)

EP Impurity B

- Steraloids (www.steraloids.com), catalog # Q2500-000, 100 mg, \$8.50 (other sizes available) (called “4-PREGNEN-17, 21-DIOL-3, 11, 20-TRIONE”)
- Research Plus (www.researchplus.com), catalog # 3269-16, 1 g and 5 g sizes (called “4-PREGNEN-17a,21-DIOL-3,11,20-TRIONE”)
- Sigma, 3 catalog entries

6 β -Hydroxy Hydrocortisone (no PHA number)

EP Impurity D

- Steraloids (www.steraloids.com), catalog # Q3730-000, 100 mg, \$700 (other sizes available) (called “4-PREGNEN-6 β , 11 β , 17, 21-TETROL-3, 20-DIONE”)
- Research Plus (www.researchplus.com), catalog # 33071-16, 5 mg and 10 mg sizes (called “4-PREGNEN-6b,11b,17a,21-TETROL-3,20-DIONE”)
- Sigma, catalog # H6904 (called “6 β -Hydroxycortisol”)

Δ^6 -Hydrocortisone (PNU-6594, SC-4647)

EP Impurity E

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Steraloids (www.steraloids.com), catalog # P0965-000, 50 mg, \$290 (one other size available)
(called “4, 6-PREGNADIEN-11 β , 17, 21-TRIOL-3, 20-DIONE”)

Reichstein’s Substance S / Deoxycortisol (PNU-1237, PNU-199997, SC-3869, CP-178660)
EP Impurity F

Steraloids (www.steraloids.com), catalog # Q1610-000, 500 mg, \$10 (other sizes available)
(called “4-PREGNEN-17, 21-DIOL-3, 20-DIONE”)

Research Plus (www.researchplus.com), catalog # 3265-16, 1 g and 5 g sizes (called “4-
PREGNEN-17a,21-DIOL-3,20-DIONE”)

Sigma, 2 catalog entries (called “Reichstein’s substance S”)