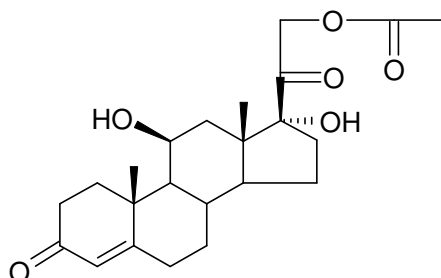


Hydrocortisone Acetate USP Micronized



C₂₃H₃₂O₆

MW 404.50

NOMENCLATURE

Pregn-4-ene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-, (11β)-
Cortisol 21-acetate

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

CAS 50-03-3

Glucocorticoid

Laboratory Code: PNU-2476

USAN, BAN, JAN: Hydrocortisone Acetate

DESCRIPTION

Hydrocortisone Acetate from Pfizer is a white to practically white, odorless, crystalline powder. It melts at about 200°C, with decomposition. It is insoluble in water; slightly soluble in alcohol and 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)		+158° to +165° (dioxane)
Loss on Drying		Not More Than 1.0%
Residue on Ignition		Not More Than 0.5% (negligible)
Chromatographic Purity		
Any Individual Impurity		Not More Than 1.0%
Total Impurities		Not More Than 2.0%
Assay (Dried Basis)		97.0% to 102.0%
Chromium		Not More Than 20 ppm
Methanol		Not More Than 0.3%
Methylene chloride		Not More Than 500 ppm
Acetone		Not More Than 0.5%

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

CHARACTERS

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

EP SPECIFICATIONS

	<u>Test</u>	<u>Specification</u>
Identification		
A. Infrared		Positive
B. Thin-layer Chromatography		Positive
Specific Optical Rotation (Dried Basis)		+158° to +167° (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 1.5%
Loss on Drying		Not More Than 0.5%
Assay (Dried Basis)		97.0% to 103.0%

Particle Size for Micronized Grades

<u>Parameter</u>	<u>Target</u>	<u>Method</u>
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

Regulatory Filings:

See Hydrocortisone acetate 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 Hydrocortisone Acetate, but Hydrocortisone Acetate from Pfizer meets the requirements of USP 26 General Chapter <467>.

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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 Acetate 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 0.5%	3: Not More Than 0.5%
Methanol	Not More Than 0.3%	2: Not More Than 3000 ppm
Methylene Chloride	Not More Than 500 ppm	2: Not More Than 600 ppm

* Pfizer does not have Registered Specifications for Residual Solvents (Total), only quality control Targets.

Other solvents used: acetic acid, dimethylformamide

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 metal known to be present in Hydrocortisone Acetate from Pfizer is Chromium, with a US Registration Specification of NMT (not more than) 20 ppm.

TSE Certificate of Suitability

Certificate No. R0-CEP 2000-353-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 Acetate. 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 Acetate 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

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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.

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 Hydrocortisone Acetate 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 Hydrocortisone Acetate.

Gluten

The raw materials used in the manufacture of Hydrocortisone Acetate 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 indicates that Hydrocortisone Acetate 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 Acetate 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 Acetate are stereoisomers of Hydrocortisone Acetate. Therefore, the stereoisomer content is LT 0.1%.