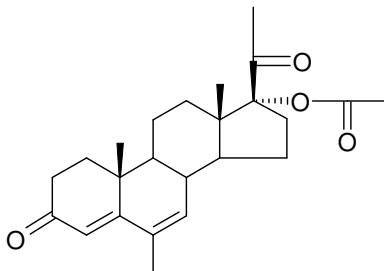


Megestrol Acetate USP

Megestrol Acetate USP Micronized



C₂₄H₃₂O₄

MW 384.51

NOMENCLATURE

Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-
 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate
 6-Methyl-3,20-dioxopregna-4,6-dien-17-yl acetate
 CAS 595-33-5

Antineoplastic

Laboratory Code: PNU-18950, SC-10363

USAN, INN, BAN: Megestrol Acetate

DESCRIPTION

Megestrol Acetate from Pfizer is a white to creamy white, tasteless and essentially odorless, crystalline powder. It is insoluble in water; sparingly soluble in alcohol; slightly soluble in ether and in fixed oils; soluble in acetone; very soluble in chloroform. It is unstable under aqueous conditions at pH 7 or above.

USP SPECIFICATIONS

<u>Test</u>	<u>Specification</u>
Completeness of Solution	Meets Test
Identification (Infrared)	Positive
Melting Range	213°C to 219°C, Range Not More Than 3°C
Specific Rotation	+8.8° to +12.0° (chloroform)
Water	Not More Than 0.5%
Residue on Ignition	Not More Than 0.2%
Heavy Metals	Not More Than 0.002%
Organic Volatile Impurities	Meets Test
Assay (Anhydrous)	97.0% to 103.0%

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

CHARACTERS

Megestrol Acetate from Pfizer is a white or almost white, crystalline powder. It is practically insoluble in water; soluble in acetone, sparingly soluble in alcohol. It melts at about 217°C.

EP SPECIFICATIONS

<u>Test</u>	<u>Specification</u>
Identification (Infrared)	Positive
Specific Optical Rotation (Dried Basis)	+14.0° to +17.0° (methylene chloride)
Related Substances	Meets Test
Impurities Profile D (Medroxyprogesterone Acetate)	Not More Than 0.5%
Total Impurities	Not More Than 1.0%
Loss on Drying	Not More Than 0.5%
Assay (Dried Basis)	97.0% to 103.0%

Regulatory Filings:

See Megestrol 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.

Megestrol Acetate 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 Megestrol 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%	
Methanol	No individual specification	2: Not More Than 3000 ppm
Methylene Chloride	Not More Than 500 ppm	2: Not More Than 600 ppm

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

Other solvents used: ethyl acetate, tetrahydrofuran

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 Megestrol Acetate from Pfizer is Palladium, with a US Registration Specification for Heavy Metals of NMT (not more than) 0.002%.

TSE Certificate of Suitability

Certificate No. R0-CEP 2000-272-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 Megestrol 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 Megestrol 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 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)

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The organism(s) currently used in the fermentation/bioconversion of plant sterols to produce intermediates that are chemically transformed into Megestrol 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 Megestrol Acetate.

Gluten

The raw materials used in the manufacture of Megestrol 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 indicate that Megestrol 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

Megestrol Acetate has six chiral carbons: C8, C9, C10, C13, C14, and C17. Pfizer's manufacturing process can modify the chirality of two of them: C9 and C17.

Stereoisomer Content

Please note that one of the known impurities of Megestrol Acetate is a stereoisomer of Megestrol Acetate. Impurity A is Δ^5 -Dihydro Megestrol Acetate, which has a quality control Target of NMT 0.2%, and an International Registration Specification of NMT 0.3%.

Commercial Availability Of API And Impurities Standards

4MPB / 6-Methylene Medroxyprogesterone Acetate (PNU-23380, SC-12164)

Impurities Profile B

EP Impurity D

Call PCS for availability of standard, may require custom synthesis

(6 β)-Medroxyprogesterone Acetate (PNU-14854, SC-10153)

Impurities Profile C

Call PCS for availability of standard, may require custom synthesis

5MPB / Medroxyprogesterone Acetate (PNU-8839, SC-9686)

EP Impurity A

EP (www.pheur.org), catalog # M0250000, 100 mg, €79

USP (www.usp.org), catalog # 1378001, 200 mg, \$150

Steraloids (www.steraloids.com), catalog # Q3021-000, 100 mg, \$10 (other sizes available)
(called "4-PREGNEN-6 α -METHYL-17-OL-3, 20-DIONE ACETATE")

Research Plus (www.researchplus.com), catalog # 3281-16, 100 mg and 1 g sizes (called "4-PREGNEN-6 α -METHYL-17 α -OL-3,20-DIONE 17-ACETATE")

Sigma, 4 catalog entries

Megestrol (PNU-11250)

EP Impurity B

Steraloids (www.steraloids.com), catalog # P0952-000, 200 mg, \$12 (other sizes available)
(called "4, 6-PREGNADIEN-6-METHYL-17-OL-3, 20-DIONE")

D-homo Megestrol Acetate (PNU-56305)

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EP Impurity C

Call PCS for availability of standard, may require custom synthesis

Δ^1 -Megestrol Acetate (no PHA number)

EP Impurity E

Call PCS for availability of standard, may require custom synthesis