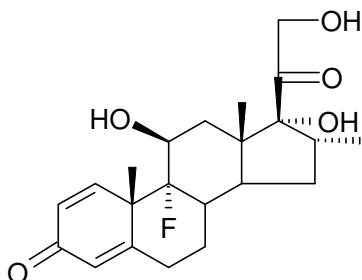




Dexamethasone USP Micronized

 $C_{22}H_{29}FO_5$

MW 392.47

NOMENCLATURE

Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl, (11 β ,16 α)-9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione

CAS 50-02-2

Glucocorticoid

Laboratory Code: PNU-19769, PNU-230076

USAN, INN, BAN, JAN: Dexamethasone

DESCRIPTION

Dexamethasone from Pfizer is a white to practically white, odorless crystalline powder. It is stable in air and melts at about 250°C, with some decomposition. It is practically insoluble in water; sparingly soluble in acetone, in alcohol, in dioxane, and in methanol; slightly soluble in chloroform; very slightly soluble in ether.

USP SPECIFICATIONS

	<u>Test</u>	<u>Specification</u>
Identification		
A. Infrared		Positive
B. Ultraviolet		Positive
Absorptivity Difference Dried Basis		Not More Than 3.0%
Specific Rotation (Dried Basis)		+72° to +80° (dioxane)
Loss on Drying		Not More Than 0.5%
Residue on Ignition		Not More Than 0.2%

USP SPECIFICATIONS (continued)

	<u>Test</u>	<u>Specification</u>
Chromatographic Purity		
Any Individual Impurity		Not More Than 1.0%
Total Impurities		Not More Than 2.0%
Organic Volatile Impurities		Meets Test



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Assay (Dried Basis)

97.0% to 102.0%

In addition to the US Registration Specifications, the following apply to Dexamethasone from Pfizer labeled "EP".

CHARACTERS

Dexamethasone from Pfizer is a white or almost white, crystalline powder. It is practically insoluble in water; sparingly soluble in ethanol, slightly soluble in methylene chloride.

EP SPECIFICATIONS

	<u>Test</u>	<u>Specification</u>
Identification		
	B. Infrared	Positive
	C. Thin-layer Chromatography	Positive
Specific Optical Rotation (Dried Basis)		+75° to +80° (dioxane)
Related Substances		Meets Test
	Any Individual Impurity	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%

Additional Tests & Particle Size for Micronized Grades

<u>Parameter</u>	<u>Target</u>	<u>Method</u>
Particle Size Less Than 20 microns	Not Less than 99%	Microscope
Particle Size Less than 10 microns	Not Less Than 75%	Microscope

Regulatory Filings:

See Dexamethasone 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.

Dexamethasone 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

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the ICH limits. Therefore, all lots of Dexamethasone 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%		
Ethyl Acetate	Not More Than 5000 ppm	3:	Not More Than 0.5%
Methylene Chloride	Not More Than 500 ppm	2:	Not More Than 600 ppm
Tetrahydrofuran	Not More Than 5000 ppm	3:	Not More Than 0.5%

* 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 Dexamethasone from Pfizer.

Chemical Certificate of Suitability

Certificate No. R0-CEP 2000-261-Rev 00 was granted to Pfizer by the European Directorate for the Quality of Medicines on 18 June 2002 for five years, for the product Dexamethasone. A copy of the certificate is available upon request.

TSE Certificate of Suitability

Certificate No. R0-CEP 2000-260-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 Dexamethasone. 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 Dexamethasone 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

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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 Dexamethasone 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 Dexamethasone.

Gluten

The raw materials used in the manufacture of Dexamethasone 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 indicates that Dexamethasone from Pfizer has only one crystal structure (or crystal form). An IR assay has been implemented to assure detection of any occurrence of undesired polymorphs.

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Chirality

Dexamethasone has eight chiral carbons: C8, C9, C10, C11, C13, C14, C16, and C17. Pfizer's manufacturing process can modify the chirality of four of them: C9, C11, C16, and C17.

Stereoisomer Content

Please note that one of the known impurities of Dexamethasone, Betamethasone, is a stereoisomer of Dexamethasone. However, Betamethasone is an impurity which is not typically present in Dexamethasone from Pfizer. Therefore, the stereoisomer content is LT 0.1%.