

API Manufacturing

The Importance of Process Understanding

When it comes to process understanding and commercial manufacturing, no other manufacturer can match Cayman's knowledge of prostaglandin chemistry. We are the industry leaders in prostaglandin synthesis with over 30 years of experience. Our expert chemists use this knowledge daily to synthesize commercially available eicosanoids as active pharmaceutical ingredients (APIs). Our talented team of scientists in Ann Arbor, Michigan, USA and Neratovice, Czech Republic has filed numerous patents for the complex synthesis and commercial manufacture of over seven APIs with additional compounds currently under development.

Cayman's Center of Excellence in Ann Arbor focuses primarily on the synthesis, scale-up, and registration of new API manufacturing processes. Once registration batches have been completed, the GMP portion of the process and all supporting documentation are transferred to our commercial manufacturing Center of Excellence in Neratovice. The facility at Cayman Pharma has over 30 years of commercial prostaglandin and eicosanoid registration and manufacturing experience, is ISO certified, and has an excellent track record with customers and regulatory authorities worldwide, including being US FDA and EMA compliant.

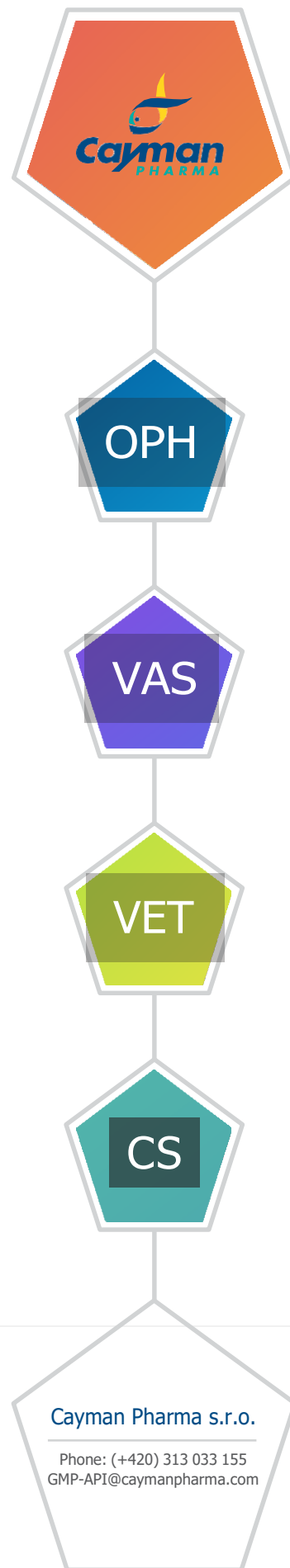
Commercial API production

We currently manufacture the following APIs according to the latest ICH and CGMP requirements for commercial distribution. Contact our sales department for more information about pricing and availability.

- CGMP Bimatoprost
- CGMP Latanoprost
- CGMP Latanoprostene Bunod
- CGMP Tafluprost
- CGMP Travoprost
- CGMP Epoprostenol Sodium Salt
- CGMP (+)-Cloprostenol Sodium Salt
- CGMP (±)-Cloprostenol Sodium Salt
- Alprostadil

Development API production

- Iloprost

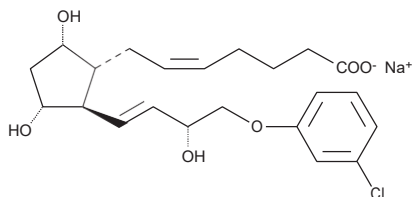


Veterinary APIs

A stable and potent analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), cloprostenol is used in the care of domestic mammals to induce luteolysis, initiate estrus, and synchronize estrus cycles. Both the racemic and active isomer are also used to induce parturition, terminate abnormal and normal pregnancies, and treat chronic endometriosis and ovarian luteal cysts.

- US FDA and EMA compliant
- Analytical standards of impurities and degradation products available

CGMP (\pm)-Cloprostenol Sodium Salt



Nomenclature

Formal Name: (\pm)-9 α ,11 α ,15R-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-prosta-5Z,13E-dien-1-oic acid, monosodium salt

CAS Number: 55028-72-3

Formula

Molecular Formula: $C_{22}H_{28}ClO_6 \cdot Na$ · Formula Weight: 446.9

Physiochemical Data

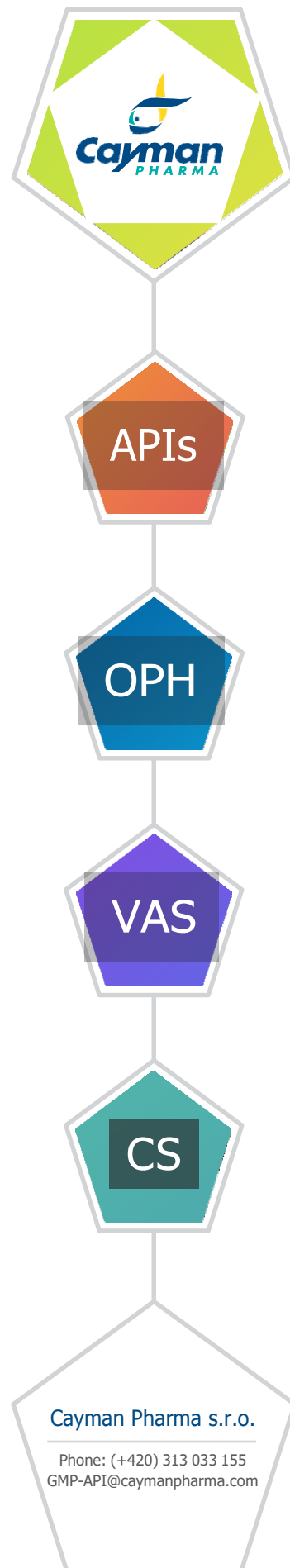
Solubility: Freely soluble in ethanol; soluble in water; practically insoluble in acetone, chloroform, diethyl ether, and hexane

Appearance: Odorless, white or off-white, slightly hygroscopic crystalline powder

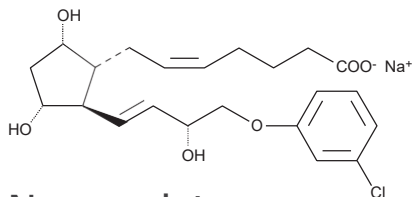
Melting Point Range: 89-104°C

Availability

GMP material which conforms to the USP and BVP Monographs is available. The DMF is on file with the US FDA, Canada, Russia, in almost all EU member states, and in many other countries.



CGMP (+)-Cloprostenol sodium salt



Nomenclature

Formal Name: (+)-9 α ,11 α ,15R-trihydroxy-16-(3-chlorophenoxy)-17,18,19,20-tetranor-prosta-5Z,13E-dien-1-oic acid, monosodium salt

CAS Number: 62561-03-9

Formula

Molecular Formula: C₂₂H₂₈ClO₆ • Na · Formula Weight: 446.9

Physicochemical Data

Solubility: Soluble in water; very soluble in ethanol; slightly soluble in acetone; practically insoluble in chloroform, diethyl ether, and hexane

Appearance: White to almost white, very hygroscopic powder

Melting Point Range: 89-104°C

Availability

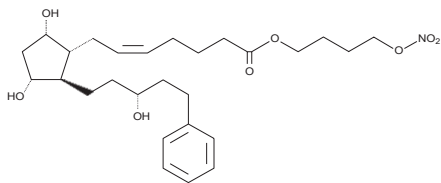
GMP material is available and the ASMF for (+)-Cloprostenol (sodium salt) is on file in the UK, Switzerland, and in most EU countries.

Ophthalmology APIs

The natural compound prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) activates signaling pathways in the eye that reduce intraocular pressure (IOP). A family of $PGF_{2\alpha}$ analogs, including bimatoprost, latanoprost, tafluprost, and travoprost, have been developed, and these compounds are more potent than $PGF_{2\alpha}$ itself in lowering IOP and have fewer side effects. Moreover, they are known to be safe and effective when used in the treatment of glaucoma.

- US FDA and EMA compliant
- Analytical standards of impurities and degradation products available

CGMP Latanoprostene Bunod



Nomenclature

Formal Name: (5Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoic acid, 4-(nitrooxy)butyl ester

CAS Number: 860005-21-6

Formula

Molecular Formula: $C_{27}H_{41}NO_8$ · Formula Weight: 507.6

Physiochemical Data

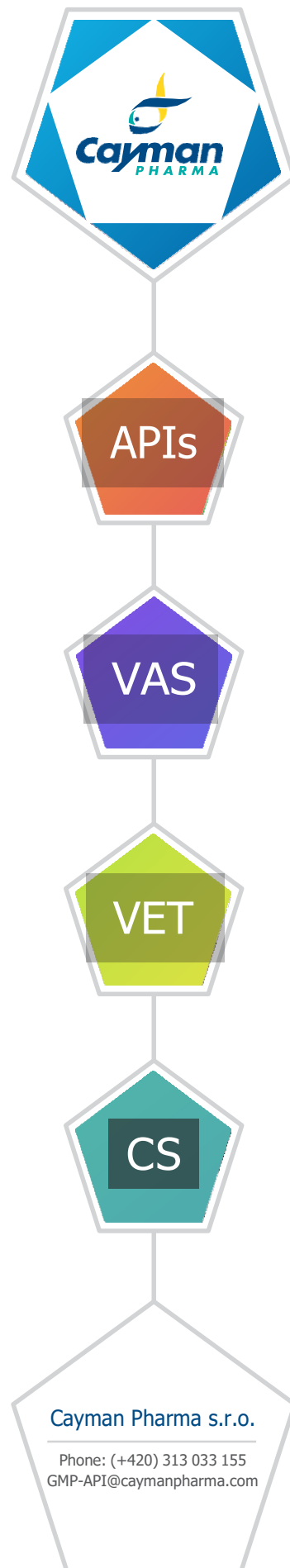
Solubility: Very soluble in acetone, ethanol, ethyl acetate, and chloroform

Appearance: Colorless to slightly yellow oil

Optical Rotation: $[\alpha]_D^{20} = +27$ to $+32^\circ$ (acetonitrile, $c = 10$ mg/ml, 589 nm)

Availability

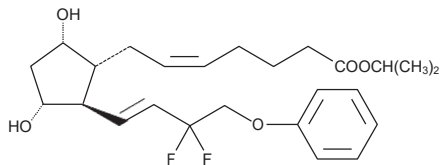
GMP material is available.



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CGMP Tafluprost



Nomenclature

Formal Name: 15,15-difluoro-9 α ,11 α -dihydroxy-16-phenoxy-17,18,19,20-tetranor-prosta-5Z,13E-dien-1-oic acid, isopropyl ester

CAS Number: 209860-87-7

Formula

Molecular Formula: C₂₅H₃₄F₂O₅ · Formula Weight: 452.5

Physiochemical Data

Solubility: Very soluble in acetone, acetonitrile, dichloromethane, diethylether, ethanol, methanol; practically insoluble in water and n-heptane

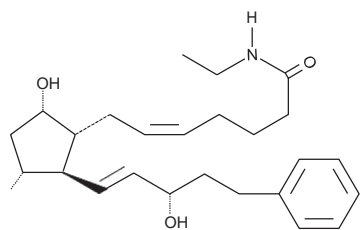
Appearance: Clear, colorless to slightly yellow oil

Optical Rotation: $[\alpha]_D^{20} = +24.0^\circ$ to $+29.0^\circ$ (CH₃CN, c = 10 mg/ml)

Availability

GMP material is available and the DMF for Tafluprost is available for customer review upon request. The DMF has been filed with the US FDA and in Russia.

CGMP Bimatoprost



Nomenclature

Formal Name: N-ethyl-9 α ,11 α ,15S-trihydroxy-17-phenyl-18,19,20-trinor-prosta-5Z, 13E-dien-1-amide

CAS Number: 155206-00-1

Formula

Molecular Formula: C₂₅H₃₇NO₄ · Formula Weight: 415.6

Physiochemical Data

Solubility: Very soluble in ethanol, methanol, dimethyl formamide, and DMSO; freely soluble in acetone; soluble in diethylene glycol; sparingly soluble in ethyl acetate; slightly soluble in water; insoluble in heptane

Appearance: White to slightly off-white crystalline powder

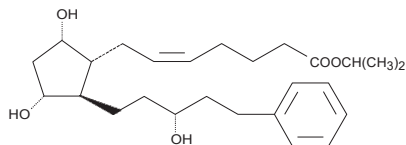
Melting Point Range: 70-72°C

Optical Rotation: $[\alpha]_D^{20} = +31.0^\circ$ to $+37.0^\circ$ (CH₃CN, c = 1,589 nm)

Availability

GMP material is available and the DMF for Bimatoprost is on file with the US FDA, Canada, and India.

CGMP Latanoprost



Nomenclature

Formal Name: 9 α ,11 α ,15R-trihydroxy-17-phenyl-18,19, 20-trinor-prost-5Z-en-1-oic acid, isopropyl ester

CAS Number: 130209-82-4

Formula

Molecular Formula: C₂₆H₄₀O₅ · Formula Weight: 432.6

Physiochemical Data

Solubility: Very soluble in ethanol, chloroform, acetonitrile, and DMSO; slightly soluble in water

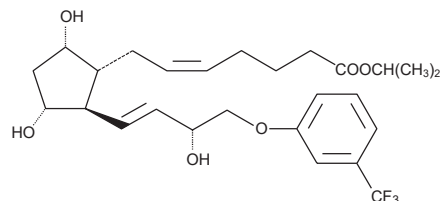
Appearance: Clear, thick, colorless to slightly yellow oil

Optical Rotation: $[\alpha]_D^{20} = +32.0^\circ$ to $+38.0^\circ$ (CH₃CN, c = 0.91, 589 nm)

Availability

GMP material which conforms to the USP and IP Monographs is available. The DMF is on file with the US FDA, Canada, India, in several EU member states, and in several other countries.

CGMP Travoprost



Nomenclature

Formal Name: (+)-9 α ,11 α ,15R-trihydroxy-16-(3-(trifluoromethyl)phenoxy)-17,18,19,20-tetranor-prosta-5Z, 13E-dien-1-oic acid, isopropyl ester

CAS Number: 157283-68-6

Formula

Molecular Formula: C₂₆H₃₅F₃O₆ · Formula Weight: 500.6

Physiochemical Data

Solubility: Very soluble in ethanol, methanol, chloroform, dichloromethane, and acetonitrile; practically insoluble in water

Appearance: Clear, colorless to slightly yellow oil

Optical Rotation: $[\alpha]_D^{20} = +14.6^\circ$ (CH₂Cl₂, c = 10 mg/ml)

Availability

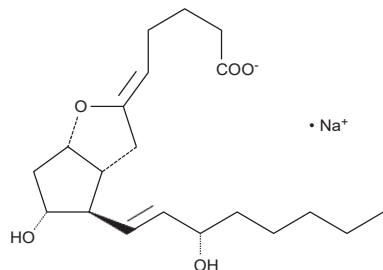
GMP material which conforms to the USP Monograph is available. The DMF is on file with the US FDA, Canada, India, Japan, China, in several EU member states, and in several other countries.

Vascular APIs

Each prostaglandin (PG) evokes distinct physiological effects through specific cell surface receptors. PGI_2 (prostacyclin) promotes smooth muscle relaxation and inhibits platelet activation through the IP receptor. Agonists of IP, including epoprostenol, iloprost, and treprostinil, are effective in relaxing pulmonary arterial smooth muscle and are used in the treatment of pulmonary hypertension.

- US FDA and EMA compliant
- Analytical standards of impurities and degradation products available

CGMP Epoprostenol Sodium Salt



Nomenclature

Formal Name: 6,9 α -epoxy-11 α ,15S-dihydroxy-prosta-5Z,13E-dien-1-oic acid, monosodium salt
CAS Number: 61849-14-7

Formula

Molecular Formula: $C_{20}H_{31}O_5 \cdot Na$ · Formula Weight: 374.5

Physiochemical Data

Solubility: Very soluble in water, ethanol, and methanol; slightly soluble in acetonitrile

Appearance: White or almost white, crystalline powder

Melting Point Range: 164.0-165.5°C (plate), 162.2-178.8°C (capillary)

Optical Rotation: $[\alpha]_D^{25} = +88^\circ$ (c = 0.8 mg/ml, $CHCl_3$) $+97^\circ$ (c = 0.8 mg/ml, 95% ethanol)

Other Data: Material is highly hygroscopic from approximately 50% RH; it is unstable in acid and neutral conditions

Availability

GMP material is available and the DMF is on file with the US FDA, Canada, Japan, Australia, and many EU member states.

