# 博士倫凡視達眼用液劑
# Vyzulta™ 0.024%, Solution

**衛部藥輸字第 027825 號**

**須由醫師處方使用**

VYZULTA™ （0.024% latanoprostene bunod 點眼液）為一種前列腺素結構類似物（prostaglandin analog）處方溶液，以無菌外用眼用溶液製劑型態供應。VYZULTA™ 含有效成分 latanoprostene bunod 及賦形劑 benzalkonium chloride、polysorbate 80、edetate disodium dihydrate、sodium citrate dihydrate、citric acid, anhydrate、glycerin、water for injection。

## 1 適應症與使用

用於開放性青光眼或高眼壓病人減輕眼內壓。

## 2 用量與使用方式

建議用量為每天使用一次、在晚間對患眼結膜囊點一滴。使用 VYZULTA™（0.024% latanoprostene bunod 點眼液）的頻率不得超過每天一次。太常使用前列腺素結構類似物可能會導致降眼內壓效果減退。

**需要同時使用 VYZULTA™ 和其他外用眼科藥品以降低眼內壓時，兩種藥品的使用須間隔至少 5 分鐘。**

## 3 劑型與劑量

VYZULTA™ 為局部外用點眼液（眼用溶液製劑），含有效成分 latanoprostene bunod 0.24 mg/mL。

## 4 禁忌症

無。

## 5 警語暨注意事項

### 5.1 色素沉積

**使用前列腺素結構類似物後，最常通報的變化為虹膜和眼周組織（眼瞼）色素沉積增加。VYZULTA™（0.024% latanoprostene bunod 點眼液）亦可能會使帶有色素的組織發生變化。**

**在使用 latanoprostene bunod 點眼液期間，預期色素沉積增加的現象會持續。色素變化是由黑色素細胞內黑色素含量增加而引起，而非此類細胞數量增加。停用 VYZULTA™ 後，虹膜色素沉積可能會永久存在，而大多數病人的眼周組織色素沉積和睫毛變化屬於可逆現象。**

供病人使用 VYZULTA™ 等前列腺素結構類似物時，應確實告知色素沉積增加（包括永久性變化）的可能性。色素沉積增加的長期影響仍為未知。

虹膜顏色變化在數個月、甚至數年間可能不甚明顯。一般而言，瞳孔周圍的褐色素沉積會呈同心圓分布，往虹膜邊緣擴散，使部分或整體虹膜的褐色變得更為明顯。虹膜色素痣和雀斑均不受此治療影響。出現明顯虹膜色素沉積的病人可繼續使用 VYZULTA™（0.024% latanoprostene bunod 點眼液），惟應定期回診接受眼科醫師檢查〔請見病人諮詢資訊 (13)〕。

### 5.2 睫毛變化

VYZULTA™ 可能會使受治療眼的睫毛和新生的毛髮逐漸發生變化，包括睫毛或毛髮長度、厚度和數量增加。睫毛變化通常在停止治療後回歸正常。

### 5.3 眼內發炎

對於有眼內發炎病史（虹膜炎／葡萄膜炎）的病人使用 VYZULTA™ 時應小心，且不應用於目前處於眼內發炎狀態的病人，否則將使病情加重。

### 5.4 黃斑水腫

前列腺素結構類似物治療期間曾獲通報黃斑水腫（包括囊樣黃斑部水腫）的案例。對於無水晶體、植入人工水晶體伴隨水晶體後囊破裂，或已知存在黃斑部水腫風險的病人，使用 VYZULTA™ 時，應更為謹慎使用。

### 5.5 細菌性角膜炎

過去曾出現使用多劑量瓶裝外用眼科產品後，發生細菌性角膜炎的案例。多數此類案例中發現病人當時使用的多劑量瓶裝外用眼科產品，已於該名病人使用前即受到患有角膜疾病或是眼表上皮表面結構受損的患處汙染。

### 5.6 搭配隱形眼鏡使用

本產品含有 benzalkonium chloride，應於使用 VYZULTA™ 前取下隱形眼鏡，並可於使用 15 分鐘後再戴上。

## 6 不良反應

標示上列有以下不良反應：

- 色素沉積〔請見警語暨注意事項 (5.1)〕
- 睫毛變化〔請見警語暨注意事項 (5.2)〕
- 眼內發炎〔請見警語暨注意事項 (5.3)〕
- 黃斑部水腫〔請見警語暨注意事項 (5.4)〕
- 細菌性角膜炎〔請見警語暨注意事項 (5.5)〕

- **戴隱形眼鏡時使用〔請見警語暨注意事項 (5.6)〕**

### 6.1 臨床試驗經驗

臨床試驗的條件相當多元，各項藥品臨床試驗中觀察到的不良反應無法與其他藥品直接互相比較，且可能無法反應臨床使用時觀察到的發生率。

兩項長達 12 個月，對 811 名病人進行 VYZULTA™ 的控制試驗評估中顯示，接受 latanoprostene bunod 治療後，最常見眼部不良反應為結膜充血（6%）、眼睛刺激（4%）、眼睛疼痛（3%）以及使用部位疼痛（2%）。約 0.6% 病人因眼睛充血、結膜刺激、眼睛刺激、眼睛疼痛、結膜水腫、視野模糊、點狀角膜炎及異物感等眼部不良反應而中斷治療。

## 7 特定族群使用

### 7.1 懷孕者

風險概要

目前仍未針對人類於孕期間使用 VYZULTA™ 的相關藥物風險評估資料。

Latanoprostene bunod 曾引起兔隻流產、小產和胎兒損傷。對孕兔經靜脈（IV）施予大於臨床 0.28 倍之 latanoprostene bunod 後，發現此物質引起流產和畸胎。自胎兔所見結構異常包括主動脈弓大血管異常、圓頂顱、胸骨與脊骨異常、肢體過度伸展及轉動異常、腹部鼓脹及水腫。以每天 150 mcg/kg 的劑量（臨床劑量的 87 倍）經靜脈使用於大鼠後，發現 latanoprostene bunod 對於大鼠不具致畸胎性〔詳見資料〕。

目前於孕期間使用此藥品與多數新生兒缺陷及流產的風險仍未知。

資料

動物資料

Latanoprostene bunod 的胚胎-胎體試驗中，以孕兔為對象，在孕期第 7~19 天間每天經靜脈注射 latanoprostene bunod 0.24~6 mcg/kg ，以對應於器官生成階段。在每天高於 0.24 mcg/kg latanoprostene bunod（臨床劑量 0.28 倍，其中依據體表面積、假定經 100%吸收）的劑量下，發生母體流產的狀況。latanoprostene bunod 治療組的胚胎胎體死亡率（胚胎再吸收）較高，其中早期吸收見於每天≥ 0.24 mcg/kg 組、晚期吸收見於每天≥ 6 mcg/kg 組（約臨床劑量 7 倍）。

在每天≥ 0.24 mcg/kg 的劑量（臨床劑量 0.28 倍）下，latanoprostene bunod 引起結構異常。型態異常包括胸骨異常、主動脈弓窄縮伴隨肺動脈幹擴張、食道後鎖骨下動脈伴隨無頭臂動脈幹、圓頂顱、前足過度伸展及後肢旋轉異常、腹部鼓脹 / 水腫，以及尾椎缺失 / 融合。

一項 latanoprostene bunod 的胚胎-胎體試驗中，以孕鼠為對象，在孕期第 7~17 天間每天經靜脈注射使用 latanoprostene bunod，恰對應於器官生成階段。使用劑量介於每天 150 至 1500 mcg/kg。在每天 1500 mcg/kg 的劑量（臨床劑量 870 倍，其中依據體表面積、假定經 100%吸收）下觀察到母體毒性（母體體重增加量減少）。

每天≥ 1500 mcg/kg 的劑量下，發現胚胎型態異常包括胸骨異常、圓頂顱、前足過度伸展與後肢旋轉異常、脊椎異常，以及肢體骨骼延後鈣化。該試驗所訂無可見不良效應濃度（NOAEL）為每天 300 mcg/kg。

### 7.2 授乳

風險概要

目前並無對於 VYZULTA™ 隨人類乳汁泌出、對於授乳嬰兒或對乳汁分泌狀況的影響的相關資料。使用前應針對整體考量哺乳對嬰兒發育和健康的益處、母親對於 VYZULTA™ 的臨床需求，以及 VYZULTA™ 對於授乳嬰兒的可能不良效應。

### 7.3 兒童用藥

**基於長期使用引起色素沉積增加的可能安全疑慮，不建議 16 歲以下的病人使用。**

### 7.4 年長者用藥

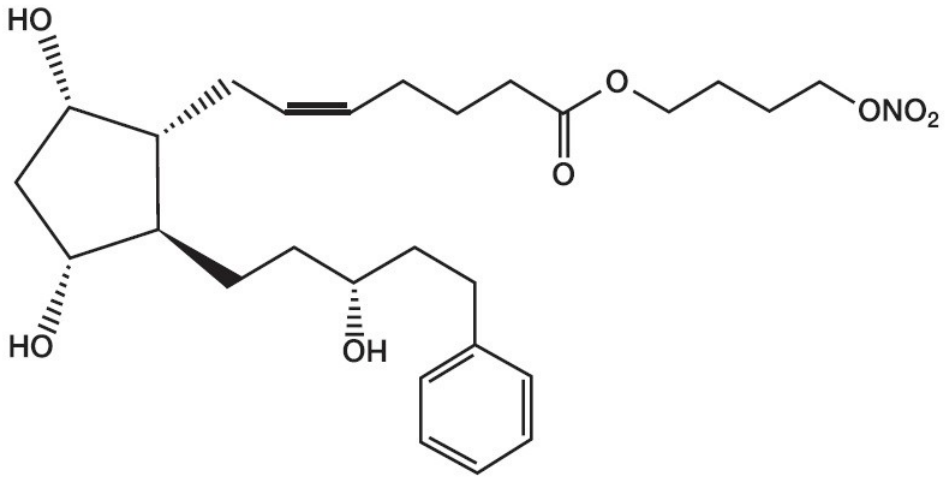
年長者和其他成年病人在安全性和效果上並無整體性的臨床差異。

## 8 說明

VYZULTA™ （0.024% latanoprostene bunod 點眼液）為一種前列腺素結構類似物（prostaglandin analog）處方溶液，以無菌外用眼用溶液製劑型態供應。VYZULTA™ 含有效成分 0.24 mg/mL latanoprostene bunod 及防腐劑 0.2 mg/mL benzalkonium chloride、界面活性劑 polysorbate 80、螯合劑 edetate disodium dihydrate (EDTA)、緩衝試劑 sodium citrate dihydrate、緩衝試劑 citric acid, anhydrate、滲透壓試劑 glycerin、water for injection，並使用緩衝溶液調整至 pH 5.5。

主成分 latanoprostene bound 為無色至黃色油狀物質，化學分子式為 $C_{27}H_{41}NO_8$。分子量：507.62。

化學結構




## 9 臨床藥理學

### 9.1 作用機制

Latanoprostene bunod 經外用於眼部後，迅速代謝為 latanoprost acid 與 butanediol mononitrate。Latanoprost acid 透過前列腺素受器的作用而增加房水經葡萄膜鞏膜通路流出，butanediol mononitrate 水解後釋放 NO，可增加房水經小樑組織流出，達到降低眼內壓的效果。眼內壓為青光眼惡化的重要風險因子，降低眼內壓可降低青光眼造成視野喪失的風險。

### 9.2 藥效學

對人類高眼內壓病人第一次投藥後約 1~3 小時，藥品會開始發揮降眼內壓的效果，並在 11~13 小時後達到最大效果。

### 9.3 藥物動力學

吸收

一項以 22 名健康受試者為對象，在 28 天期間每天早晨使用一次 VYZULTA™ 外用點眼液（雙眼各一滴），以評估 latanoprostene bunod 及其代謝物 latanoprost acid 及 butanediol mononitrate 的全身性暴露量的試驗。在用藥後第 1 天和第 28 天，latanoprostene bunod（定量下限 [LLOQ] 為 10.0 pg/mL）或 butanediol mononitrate （LLOQ 為 200 pg/mL）在血漿中的濃度都未達可測得的程度。Latanoprost acid（LLOQ 為 30 pg/mL）在第 1 天和第 28 天的平均最高血漿濃度（$C_{max}$）分別為 59.1 pg/mL 和 51.1 pg/mL。

Latanoprost acid 的達最高血漿濃度平均時間（$T_{max}$）在第 1 天及第 28 天均約 5 分鐘。

分布

目前仍無人類的眼部分布試驗。

代謝

經外用於眼部後，latanoprostene bunod 會在眼內迅速代謝為 latanoprost acid（活性成分），為一種 F2$\alpha$ 前列腺素結構類似物以及 butanediol mononitrate。Latanoprost acid 進入全身循環後，主要由肝臟經脂肪酸 $\beta$-氧化作用代謝為 1,2-dinor 及 1,2,3,4-tetranor 代謝物。

Butanediol mononitrate 會代謝為 1,4-butanediol and nitric oxide，其中 1,4-butanediol 會進一步氧化為 succinic acid，並進入檸檬酸（TCA）循環。

排除

Latanoprost acid 會迅速從人類血漿排除。大部分人類受試者在眼部使用 VYZULTA™ 15 分鐘後，latanoprost acid 血漿濃度降至低於 30 pg/mL（LLOQ）。

## 10 非臨床毒理學

### 10.1 致癌性、致突變性、生育力受損

Latanoprostene bunod 對於細菌不具致突變性，於大鼠體內微核分析試驗中不具有遺傳毒性。在無生物活化影響下的體外試驗中，發現人類淋巴球出現染色體變異。

長期動物試驗並未探討 latanoprostene bunod 的致癌性。Latanoprost acid 為 latanoprostene bunod 的主要代謝物之一。經嚙齒動物的經口使用終生生物試驗，大鼠和小鼠暴露於 latanoprost acid 後顯示該物質不具致癌性。

之前未對 latanoprostene bunod 進行生育力試驗。探討生育力影響的可能性時，可利用 latanoprost acid 的暴露結果，該物質為 latanoprostene bunod 及 latanoprost 的常見代謝物。動物試驗並未發現 latanoprost acid 對於雄性和雌性個體生育力的任何影響。

### 10.2 動物毒性及／或藥理學

在一項為期 9 個月的毒性試驗中，對馬來猴的一眼施予含 latanoprostene bunod 的外用眼藥，另一眼施以對照組（僅含基質），對試驗眼以每天兩次各一滴 0.024% latanoprostene bunod，每天兩次各一滴 0.04% latanoprostene bunod，以及每天兩次各兩滴 0.04% latanoprostene bunod，其全身性暴露量分別相當於臨床劑量的 4.2、7.9 和 13.5 倍（其中依據體表面積、假定 100%吸收）。在 9 個月後的顯微鏡觀察評估中，0.04% 雄性組出現坐骨神經退化，但與藥物之間的關係尚不清楚。

## 11 臨床試驗

在長達 12 個月的臨床試驗中，以開放型青光眼或平均基礎眼內壓（IOP）達 26.7 mmHg 的高眼壓病人為對象，每天（在晚間）使用一次 VYZULTA™（0.024% latanoprostene bunod 點眼液）後，眼內壓下降量

可達 7~9 mmHg。

**12　供應 / 儲存及管理方式**

VYZULTA™( 0.024% latanoprostene bunod 點眼液 )以附滴瓶瓶嘴的塑膠瓶及青色瓶蓋供應，其容量如下：

4 mL 瓶裝、內容物 2.5 mL - NDC 24208-504-02
7.5 mL 瓶裝、內容物 5 mL - NDC 24208-504-05

保存

未開啟的藥瓶應放入 2°~8°C (36°~46°F) 環境保存。藥瓶開封後，可在低於 25°C (77°F) 的環境下保存 8 週。

運送藥瓶時，可將藥瓶保存在 40°C (104°F) 以下的環境，且保存時間不得超過 14 天。

**請避免光照。請避免冷凍。**

**13　病人諮詢資訊**

- **色素沉積可能性**

**應向病人說明虹膜可能出現褐色素沉積增加，且可能成為不可逆反應的可能性。另外，也應向病人說明眼瞼皮膚暗沉的可能性，但通常會在停用 VYZULTA™ 後回歸正常。**

- **睫毛變化可能性**

**應向病人說明在 VYZULTA™ 治療期間，治療眼的睫毛和新生毛可能會出現變化。這些變化可能會導致雙眼睫毛或新生毛的長度、厚度、色素沉積、數量及／或生長方向出現差異。**

**睫毛變化通常在停止治療後回歸正常。**

- **藥瓶處理**

**應向病人說明避免使藥瓶滴嘴接觸眼睛、周圍結構、手指或其他表面，否則可能會受到眼部感染常見菌種的汙染。使用受汙染的液劑可能會導致眼睛嚴重受損、甚至失明。**

- **就醫時機**

**請向病人說明：出現新的眼睛問題（創傷或感染）、視力急速下滑、接受眼部手術，或發生任何眼部反應（特別是結膜炎和眼瞼反應）時，應立即向醫師詢問是否可繼續使用 VYZULTA™。**

- **關於隱形眼鏡使用者**

**請在使用外用點眼液劑前取下隱形眼鏡，並在使用完畢 15 分鐘後再戴上鏡片。**

- **與其他眼科藥品使用**

**需要使用超過一種外用眼科藥品時，使用每種藥品之間應間隔至少 5 分鐘。**

美國專利號：7,273,946、7,629,345、7,910,767、8,058,467

Vyzulta™ 為博士倫（Bausch & Lomb Incorporated）或其附屬公司之商標。



製造廠名稱：Bausch & Lomb Incorporated

製造廠地址：8500 Hidden River Parkway, Tampa, FL 33637

藥商：博士倫股份有限公司

地址：10682 台北市大安區敦化南路二段 95 號 16 樓

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use VYZULTA safely and effectively. See full prescribing information for VYZULTA.**

**VYZULTA (latanoprostene bunod ophthalmic solution) 0.024%, for topical ophthalmic use**
**Initial U.S. Approval: 2017**

**---------- INDICATIONS AND USAGE ----------**
VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

**---------- DOSAGE AND ADMINISTRATION ----------**
One drop in the affected eye(s) once daily in the evening. (2)

**---------- DOSAGE FORMS AND STRENGTHS ----------**
Topical ophthalmic solution: 0.24 mg/mL latanoprostene bunod (0.024%) (3)

**---------- CONTRAINDICATIONS ----------**
None. (4)

**---------- WARNINGS AND PRECAUTIONS ----------**
- Pigmentation: Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. (5.1)
- Eyelash changes: Gradual changes to eyelashes including increased length, increased thickness and number of eyelashes. Usually reversible upon discontinuation of treatment. (5.2)

**---------- ADVERSE REACTIONS ----------**
Most common ocular adverse reactions with incidence ≥ 2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 11/2017**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## 2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the conjunctival sac of the affected eye(s) once daily in the evening**.** Do not administer VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% more than once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect.

If VYZULTA is to be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, administer each drug product at least five (5) minutes apart.

## 3 DOSAGE FORMS AND STRENGTHS

VYZULTA is a topical ophthalmic solution containing latanoprostene bunod, 0.24 mg/mL.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17)]*.

### 5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

### 5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

### 5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

### 5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

### 5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

## 6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Pigmentation *[see Warnings and Precautions (5.1)]*
- Eyelash Changes *[see Warnings and Precautions (5.2)]*
- Intraocular Inflammation *[see Warnings and Precautions (5.3)]*
- Macular Edema *[see Warnings and Precautions (5.4)]*
- Bacterial Keratitis *[see Warnings and Precautions (5.5)]*
- Use with Contact Lens *[see Warnings and Precautions (5.6)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and

vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose)*[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

*Animal Data*

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

### 8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

### 8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

### 8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

## 11 DESCRIPTION

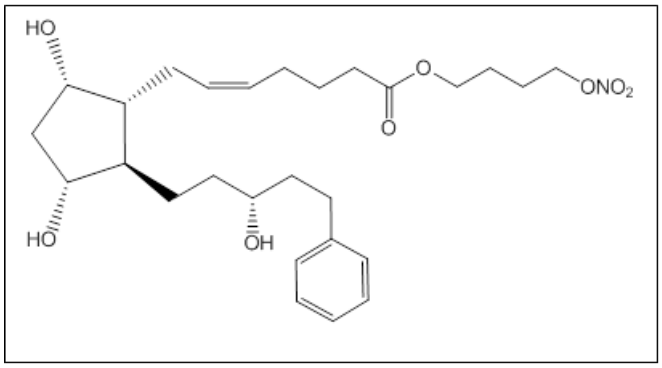
VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin analog formulated as a sterile topical ophthalmic solution. VYZULTA contains the active ingredient latanoprostene bunod 0.24 mg/mL, the

preservative benzalkonium chloride 0.2 mg/mL, and the following inactive ingredients: polysorbate 80, glycerin, EDTA, and water. The formulation is buffered to pH 5.5 with citric acid/sodium citrate.

Its chemical name is 4-(Nitrooxy)butyl (5Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate. Its molecular formula is $C_{27}H_{41}NO_8$. Molecular weight: 507.62.

Its chemical structure is:

Figure 1




Latanoprostene bunod is a colorless to yellow oil.

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

Latanoprostene bunod is thought to lower intraocular pressure by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Intraocular pressure is a major modifiable risk factor for glaucoma progression. Reduction of intraocular pressure reduces risk of glaucomatous visual field loss.

## 12.2 Pharmacodynamics

Reduction of the intraocular pressure starts approximately 1 to 3 hours after the first administration with the maximum effect reached after 11-13 hours in eyes with elevated intraocular pressure.

## 12.3 Pharmacokinetics

*Absorption*

The systemic exposure of latanoprostene bunod and its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects after topical ocular administration of VYZULTA 0.024% once daily (one drop bilaterally in the morning) for 28 days. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of quantitation, LLOQ, of 10.0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post dose on Day 1 and Day 28. The mean maximal plasma concentrations (Cmax) of latanoprost acid (LLOQ of 30 pg/mL) were 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time of maximal plasma concentration (Tmax) for latanoprost acid was approximately 5 min post administration on both Day 1 and Day 28.

*Distribution*

There were no ocular distribution studies performed in humans.

*Metabolism*

After topical ocular administration, latanoprostene bunod is rapidly metabolized in the eye to latanoprost acid (active moiety), an F2 $\alpha$ prostaglandin analog, and butanediol mononitrate. After latanoprost acid reaches the systemic circulation, it is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Butanediol mononitrate is metabolized to 1,4-butanediol and nitric oxide. The metabolite 1,4-butanediol is further oxidized to succinic acid and enters the tricarboxylic acid (TCA) cycle.

*Elimination*

The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30 pg/mL) in the majority of subjects by 15 min following ocular administration of VYZULTA 0.024% in humans.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

## 13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

# 14 CLINICAL STUDIES

In clinical studies up to 12 months duration, patients with open-angle glaucoma or ocular hypertension with average baseline intraocular pressures (IOPs) of 26.7 mmHg, the IOP-lowering effect of VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% once daily (in the evening) was up to 7 to 9 mmHg.

# 16 HOW SUPPLIED/STORAGE AND HANDLING

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is supplied in a natural low density polyethylene, 7.5 mL bottle with dropper tip and a turquoise cap filled with a 5 mL fill volume (NDC 24208-504-05).

*Storage:* Unopened bottle should be stored refrigerated at 2º to 8ºC (36º to 46ºF). Once a bottle is opened it may be stored at 2º to 25ºC (36º to 77ºF) for 8 weeks.

During shipment, bottles may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days.

**Protect from light. Protect from freezing.**

# 17 PATIENT COUNSELING INFORMATION

- *Potential for Pigmentation*

  Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which is usually reversible after discontinuation of VYZULTA.

- *Potential for Eyelash Changes*

  Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with VYZULTA. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

- *Handling the Container*

  Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

- *When to Seek Physician Advice*

  Advise patients that if they develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of VYZULTA.

- *Use with Contact Lenses*

  Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of VYZULTA.

- *Use with Other Ophthalmic Drugs*

  If more than one topical ophthalmic drug is being used, the drugs should be administered with at least five (5) minutes between applications.

U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.

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**Distributed by:**
Bausch + Lomb, a division of
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

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JOHN J FARLEY
11/02/2017