Taiwan Food and Drug Administration

Assessment Report

Trade Name：博士倫凡視達眼用液劑/ Vyzulta 0.024%, solution

Active Ingredient：Latanoprostene bunod

License Number：MOHW-PI 027825

Applicant：博士倫股份有限公司

Approval Date：2020/02/26

Indication：用於開放性青光眼或高眼壓病人減輕眼內壓。

VYZUTA is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Background Information

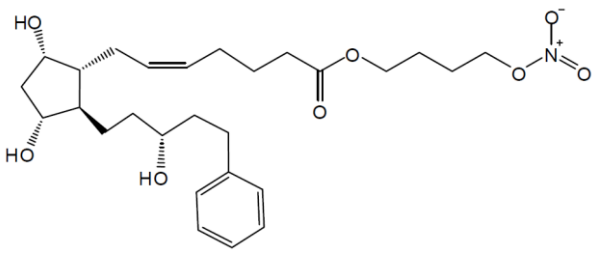
Trade Name	博士倫凡視達眼用液劑/ Vyzulta 0.024%, solution
Active Ingredient(s)	Latanoprostene bunod
Applicant	博士倫股份有限公司
Dosage Form & Strengths	點眼液劑 0.24 mg/mL
Indication	用於開放性青光眼或高眼壓病人減輕眼內壓。 VYZUTA is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
Posology	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.
Pharmacological Category **ATC Code**	S01EE06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Latanoprostene bunod is used as the drug substance of Vyzulta™ (latanoprostene bunod ophthalmic solution) 0.024%.



The molecular formula and the molecular weight are $C_{27}H_{41}NO_8$ and 507.62 g/mol, respectively. It's a colorless to pale yellow viscous oil.

The structure of latanoprostene bunod is confirmed by ^{1}H-NMR, ^{13}C-NMR, mass spectrum and FTIR spectrum.

The specification includes tests for appearance, identification, water content, residue on ignition, assay, related substances, isomeric impurities, total impurities, specific rotation and residual solvents.

2.1.2 Drug product

Drug product is an ophthalmic solution provided at 0.24 mg/mL of drug substance and packaged in a low density polyethylene (LDPE) bottle. The excipients used in the drug product formulation comply with the compendial monographs. No animal/human origins are used in the formulation. The established operating parameters and test results for manufacturing process are suitable.

Adequate release and shelf-life specification have been presented for the drug product. The test items include appearance, identification, assay, related substances, benzalkonium chloride, pH, osmolality, particulate matter, antimicrobial effectiveness, sterility, weight loss/again and fill volume. Analytical methods are described and well validated.

Stability studies of drug product under long term condition (2-8℃) and accelerated condition (25℃/40% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Vyzulta® (latanoprostene bunod, 0.024%) ophthalmic solution is a drug for the reduction of intraocular pressure in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Latanoprostene bunod, upon topical ocular administration, is metabolized to two active moieties, the prostaglandin F receptor agonist latanoprost acid (LA) and the NO-donating moiety butanediol mononitrate (BDMN). The *in vitro* pharmacodynamics

studies showed that latanoprost and NO-donating moiety of latanoprostene bunod presented effects on their target pathways, respectively. The *in vivo* studies showed that topical administration of latanoprostene bunod lowered intraocular pressure in rabbits, dogs and monkeys. The effect of latanoprostene bunod was better than latanoprost.

2.2.2 Toxicological Studies

The pivotal studies included a 4-week and a 9-month repeated-dose toxicity studies. There was no test-article-related finding after topical administration of latanoprostene bunod at 48 μg/day. Latanoprostene bunod presented negative results in Ames test and *in vivo* micronucleus assay presented positive result in chromosome aberration assay, which was the same as latanoprost. It suggested that LA has the potential to inhibit mitosis and to induce chromosome aberration. The carcinogenicity of latanoprost and naproxcinod (a drug which also has BDMN as its NO-donating moiety) was evaluated. No unusual tumor types or increased incidences of tumors were observed.

Intravenous administration of latanoprostene bunod presented teratogenic potential in both rats and rabbits. This teratogenic potential might be due to LA since the NOAEL values of latanoprostene bunod were similar to latanoprost. In addition, both latanoprost and naproxcinod did not present any effect on pre- and post-natal development.

The toxicity of two impurities (15s BOL-303259-X and 5,6-trans BOL-303259-X) was evaluated by topical dosing with latanoprostene bunod containing high levels of impurities. As compared to the pivotal 28-day and 9-month studies, no new toxicity or effects were observed.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Latanoprostene bunod (LBN) is a product and rapidly metabolized to two active moieties in eye, latanoprost acid and butanediol mononitrate (BDMN). The bioavailability was evaluated in 22 healthy volunteers after ocular administration of Vyzulta 0.024% QD bilaterally for 28 days. Only latanoprost acid was quantifiable. The C_{max} of latanoprost acid were 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively.

There was no ocular distribution studies performed in humans. After latanoprost acid reached the systemic circulation, it is primarily metabolized by liver. BDMN is metabolized to 1,4-butanediol and NO, and then further enters the TCA cycle.

The plasma level of latanoprost dropped below the LLOQ by 15 minutes following ocular administration in humans.

2.3.2 Interaction Studies

The DDI studies of LBN were not evaluated. There was low potential of LBN and its metabolites to be interacted with isozymes of CYP450.

2.3.3 Special Populations

No clinical studies have been conducted to specifically analyze the effect of race, age, sex, or hepatic or renal impairment on the PK of LBN, LA, and BDMN in plasma. It was unlikely that elimination of LBN would be significantly impacted in organ compromised individuals because the low systemic exposure of LBN and its metabolites.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study [769] and Study [770] were provided to support the efficacy of Vyzulta for the claimed indication. The primary objective of the two studies was to demonstrate the non-inferiority of Vyzulta to Timolol maleate 0.5% with respect to the reduction of IOP.

The primary efficacy endpoint was the mean IOP in the study eye measured at the specified time points: 8 AM, 12 PM, and 4 PM at Week 2, Week 6 and Month 3. Non-inferiority of Vyzulta to Timolol will be established if the upper limit of the 95% CI for the difference in the mean IOP was < 1.5 mmHg at each 9 time points and was < 1 mmHg in 5 of the 9 time points. If non-inferiority is established, the superiority of Vyzulta over Timolol will be tested as a secondary objective. Superiority of Vyzulta to Timolol will be established if the upper limit of the 95% CI for the difference in the mean IOP was < 0 mmHg for all 9 time points.

In both studies, Vyzulta demonstrated non-inferiority to Timolol in IOP reduction at all 9 pre-specified time points. However, the statistical superiority of Vyzulta over Timolol was not established in at least one time point.

The IOP lowering effect of Vyzulta was further evaluated based on two key secondary endpoints: the proportion of subjects with IOP $\leqq$ 18 mmHg consistently at all 9 time points and the proportion of subjects with IOP reduction $\geqq$ 25% consistently at all 9 time points. Multiplicity due to using the two endpoints will be adjusted using the Hochberg method.

The Vyzulta group had a significantly higher proportion of subjects who attained an IOP $\leqq$ 18 mmHg at all 9 time point in Study [769], but the difference was not statistically significant in Study [770]. The proportion of subjects with an IOP reduction of $\geqq$ 25% from baseline consistently at all 9 time points was significantly higher in the Vyzulta group in both studies.

As a result, the two Phase III studies have provided adequate evidence of efficacy to support the indication of the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OH) for once daily use of Vyzulta.

2.4.2 Safety Results

The mean duration of exposure for all subjects treated with any Vyzulta was 138.6 days. Out of the entire safety population (at least 1 dose of LBN ophthalmic solution), at least 297 subjects with OHT or OAG were exposed at least 365 days and at least 746 subjects with OHT or OAG were exposed at least 180 days.

Approximately 0.6% of subjects discontinued therapy because of ocular adverse reactions (ocular hyperemia 0.2%, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation 0.1% each).

The most common ocular adverse reactions observed in the 811 subjects treated with LBN ophthalmic solution 0.024% in Study769 and 770 were conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%).
Warnings and precautions of Vyzulta include pigmentation, eyelash changes, intraocular inflammation, macular edema, bacterial keratitis and use with contact lens, all of which are disclosed in the label.

2.5 Bridging Study Evaluation

Vyzulta (latanoprostenet bound, LBN) is a prodrug, which would rapidly be metabolized to two active moieties, latanoprost acid and BDMN. Only plasma level of latanoprost acid was available. Although Japanese healthy volunteers possess 3-fold higher level of latanoprost acid as compared to that of western population following single and multiple ocular administration of LBN ophthalmic solution 0.024% QD, the overall systemic exposure was considered extremely low. Regarding similar ocular hypotensive effect in Japanese and Caucasians, it was considered none to minimally ethnically sensitive.

There are total 271 subjects in three Japanese studies. In the clinical development program of Vyzualta, Study 811 is an open label study which consisted of a 52-weeks period to collect long-term safety data and information about IOP. The study results showed similar effect of reduction of IOP in Study 811, compared to that in the pivotal studies. Regarding the safety profile, most of the adverse events belong to the class effect of prostaglandin analogs reported in the literature.

Accordingly, considering the extremely low potential of systemic exposure of Vyzualta , similar ocular hypotensitve effect, the effect and safety in the East Asians and available

prostaglandin analog Xalatan(latanoprost), the waiver of BSE of Vyzulta is granted.

2.6 Conclusion

Based on available information, the submitted dossiers in the CMC, PT, PK, clinical and statistical sections are assessed acceptable. The overall benefit/risk ratio of Vyzulta 0.024% once daily is positive in the treatment of patients with open-angle glaucoma or ocular hypertension. Approval is recommended.

3. Post-Marketing Requirements

Routine pharmacovigilance should be conducted