CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January – February

BRAND NAME
Vyzulta®

GENERIC NAME
Latanoprostene Bunod

MANUFACTURER
Bausch & Lomb Incorporated

DATE OF APPROVAL
November 2, 2017

PRODUCT LAUNCH DATE
Currently commercially available

REVIEW TYPE
☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)[1]
Vyzulta is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

OFF LABEL USES
Not applicable

CLINICAL EFFICACY[1,2]
Background

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Glaucoma is the second leading cause of blindness worldwide. In 2015, OAG waas estimated to affect approximately 2.2 million people in the United States, with projections to 3.3 million in 2020. A key goal of therapy is to reduce and maintain IOP within a target range that is individualized for the patient. Lowering IOP can delay or prevent damage to optic nerves and can reduce the risk of vision loss even in patients who are considered to have normal IOP.

Prostaglandin analogs are considered the first line therapy due to high efficacy, relative safety, and ease of administration (once daily). Other therapies include beta-blockers, alpha-adrenergic agonists, parasympathomimetic agents, and carbonic anhydrase inhibitors.

Vyzulta is a prostaglandin analog that is metabolized into two moieties, lowering IOP through a dual mechanism of action. The latanoprost acid moiety increases outflow of aqueous humor through the uveoscleral pathway, while the butanediol mononitrate moiety releases nitric oxide to increase outflow through the trabecular meshwork and Schlemm's canal.

	APOLLO[3,4]
Study Design	Phase 3, randomized, multicenter, double-blind, active-controlled study Inclusion criteria: • Age ≥18 years • Diagnosis of OAG or OHT in ≥1 eye • Intraocular pressure ≥22 and ≤36 mmHg after washout period • Best-corrected visual acuity (BCVA) of +0.7 logarithm of the minimum angle of resolution (logMAR) units or better in either eye Exclusion criteria: • Central corneal thickness >600 um or other condition preventing reliable applanation tonometry • Advanced glaucoma (Cup-to-disk ratio >0.8 or split fixation) • Need or anticipated need for treatment with corticosteroids or need to initiate or modify medication known to affect IOP
N	N=420 (Latanoprostene (LBN), n=286; timolol, n=134)
Drug Regimen	LBN 0.024% once every evening vs. Timolol maleate 0.5% twice daily
Primary Outcome(s)	• Non-inferiority based on IOP within ± 1.5 mmHg of the latanoprost group at each of the 9 assessment time points • If non-inferiority was achieved, superiority was determined if upper limit of 95% CI did not exceed 0 mmHg at all 9 time points.
Secondary Outcome(s)	• Proportion of subjects with IOP ≤18 mmHg consistently at all 9 time points • Proportion of subjects with IOP reduction ≥25% consistently at all 9 time points

Results	• Mean IOP was lower with LBN compared to timolol at all 9 time points
	  • Range of mean difference: -1.0 to -1.4 mmHg, P ≤0.002
	  • Uppermost limit of 95% CI's across all time points = -0.4 mmHg

	• Percentage of subjects with IOP ≤18 mmHg and IOP reduction ≥25% was significantly higher in the LBN group vs timolol group.
	  • IOP ≤18 mmHg: 22.9% vs 11.3%,
	  Difference: 11.6% (95% CI, 4.3-18.9; P=0.005)
	  • IOP reduction ≥25%: 34.9% vs 19.5%, P=0.001
	  Difference: 15.3% (95% CI, 6.6-24.0; P=0.001)
	*Similar results were produced in the phase 3 LUNAR trial

# Withdrew due to Lack of Efficacy	Not reported
# Withdrew due to Adverse Effects	LBN, n=4 (<1%) Timolol, n=4 (2.9%)

	VOYAGER[5]
Study Design	Phase 2, randomized, multicenter, double-blind, active-controlled, dose-ranging study Inclusion criteria: • Age ≥18 years • Diagnosis of OAG or OHT in ≥1 eye • IOP of 22-36 mmHg, with 2 of 3 baseline measurements ≥24 • Best-corrected visual acuity (BCVA) of +0.7 logarithm of the minimum angle of resolution (logMAR) units or better in either eye Exclusion criteria: • Central corneal thickness >600 um or other condition preventing reliable applanation tonometry • Advanced glaucoma (Cup-to-disk ratio >0.8 or split fixation) • Need or anticipated need for treatment with corticosteroids or need to initiate or modify medication known to affect IOP
N	N=413 (LBN 0.006%, n=82; LBN 0.012%, n=85; LBN 0.024%, n=83; LBN 0.040, n=81; Latanoprost, n=82)
Drug Regimen	LBN 0.006%, 0.012%, 0.24%, 0.040% vs Latanoprost 0.005% once every evening
Primary Outcome(s)	Change from baseline (CFB) in mean diurnal IOP at visit 6 (day 28)
Secondary Outcome(s)	Change in mean diurnal IOP at days 7, 14, and 29
Results	• Efficacy of LBN was dose dependent, CFB of mean IOP at day 28 plateaued between LBN 0.024% and 0.040%, and resulted in greater lowering of IOP vs latanoprost 0.005%. • LBN 0.024%: CFB = 9.0 mmHg

	○ Difference vs latanoprost: 1.23 mmHG (95% CI 0.37-2.10, p=0.005) • LBN 0.040%: CFB = 8.93 mmHg ○ Difference vs latanoprost: 1.16 mmHG (95% CI 0.29-2.03, p=0.009) • Latanoprost 0.005%: CFB = 7.77 mmHg • LBN 0.024% achieved greater reductions in mean diurnal IOP compared to latanoprost at days 7, 14, and 29. • Day 7: CFB = 0.98 (95% CI 0.08-1.88, p=0.033) • Day 14: CFB = 1.14 (95% CI 0.23-2.05, p=0.015) • Day 29: CFB = 0.95 (95% CI 0.00-1.91, p=0.051) [36-44h after final dose]
# Withdrew due to Lack of Efficacy	Not reported
# Withdrew due to Adverse Effects	LBN, n=2 (<1%) Latanoprost, n=0

CONTRAINDICATIONS
Not applicable

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
Not applicable

ADVERSE REACTIONS
The most common ocular adverse reactions with incidence ≥ 2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). In addition, Vyzulta has warnings for increased eye pigmentation of the iris and periorbital tissue as well as eyelash changes.

DOSAGE AND ADMINISTRATION
Vyzulta is given one drop in the conjunctival sac of the affected eye(s) once daily in the evening. Do not administer more than once daily as more frequent administration of prostaglandin analogs may lessen the IOP lowering effect. If Vyzulta is used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

PRODUCT AVAILABILITY
Ophthalmic solution: 0.024% (5 mL)

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THERAPEUTIC ALTERNATIVES[6]

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
latanoprost (Xalatan®)	1 drop in the affected eye(s) once daily in the evening	
timolol (Timoptic®)	1 drop in the affected eye(s) BID	
brimonidine (Alphagan® P)	1 drop in the affected eye(s) TID	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation
• There is not significant potential for inappropriate use.
Product Comparison
• CPAC score: 70 vs Timolol – Modest benefits over current therapies • CPAC score: 65 vs Latanoprost – Modest benefits over current therapies • It would be clinically appropriate to provide equal access to Vyzulta, ophthalmic prostaglandin analogs, ophthalmic beta-blockers, and ophthalmic alpha-2 adrenergic agonists, or to require a trial of one before the others.

REFERENCES

[1] Vyzulta Prescribing Information. Bridgewater, NJ: Bausch & Lomb Incorporated; November 2017. Available at: www.bausch.com. Accessed November 20, 2017.
[2] Primary Open-Angle Glaucoma Preferred Practice Pattern® Guidelines. Available at: www.aaojournal.org. Accessed November 20, 2017.
[3] Weinreb R, Sforzolini B, Vittitow J, et al. Latanoprostene Bunod 0.024% versus Timolol Maleate 0.5% in Subjects with Open-Angle Glaucoma or Ocular Hypertension: The APOLLO Study. Ophthalmology 2016; 123(5):965-973.
[4] Medeiros F, Martin K, Peace J, et al. Comparison of Latanoprostene Bunod 0.024% and Timolol Maleate 0.5% in Open-Angle Glaucoma or Ocular Hypertension: The LUNAR Study. Am J Ophthalmol 2016; 168:250-259.
[5] Weinreb R, Ong T, Sforzolini B, et al. A randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol 2015; 99:738-745.
[6] Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 20, 2017.