**Draft Guidance on Latanoprost**



**Active Ingredient:** Latanoprost

**Dosage Form; Route:** Emulsion; ophthalmic

**Strength:** 0.005%

**Recommended Study:** One study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized (1:1), double-masked, parallel, two-arm, in vivo
Strength: 0.005%
Subjects: Males and females with chronic open angle glaucoma or ocular hypertension in both eyes
Additional comments: Specific recommendations are provided below

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**Analytes to measure (in appropriate biological fluid):** Not applicable

**Bioequivalence based on (95% CI)**: Clinical endpoint

**Additional comments regarding the BE study with clinical endpoint:**

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of open angle glaucoma and ocular hypertension comparing the test product to the reference standard (RS) product, each applied as one drop in both eyes once daily in the evening for 42 days (6 weeks).

2. Inclusion criteria (the applicant may add additional criteria):
    a. Male or nonpregnant females aged at least 18 years with chronic open angle glaucoma or ocular hypertension in both eyes.
    b. Subject requires treatment of both eyes and is able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period.
    c. Adequate wash-out period prior to baseline of any ocular hypotensive medication (see Table 1). In order to minimize potential risk to patients due to intraocular pressure (IOP) elevations during the washout period, the investigator may choose

to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a sympathomimetic, alpha-agonist, beta-adrenergic blocking agent, or prostaglandin; however, all patients must have discontinued all ocular hypotensive medication for the minimum washout period provided in Table 1.

d. Baseline (Day 0/hour 0) IOP ≥ 22 mm Hg and ≤ 34 mm Hg in each eye and any asymmetry of IOP between the eyes no greater than 5 mm Hg.
e. Baseline best corrected visual acuity equivalent to 20/200 or better in each eye.

**Table 1: Washout Periods for Ocular Hypotensive Medications**

| **Medication** | **Minimum Washout Period** |
|---|---|
| Parasympathomimetics [e.g., pilocarpine (Isopto® Carpine), carbachol (Isopto® Carbachol)] | 4 days |
| Carbonic anhydrase inhibitors (systemic or topical) [e.g., acetazolamide (Diamox®), dorzolamide hydrochloride (Trusopt®), brinzolamide (Azopt®)] | 4 days |
| Sympathomimetics [e.g., dipivefrin (Propine®), epinephrine (Epifrin®)] | 2 weeks |
| Alpha-agonists [e.g., apraclonidine (Iopidine®), brimonidine tartrate (Alphagan®, Alphagan® P), brimonidine tartrate and brinzolamide (Simbrinza®)] | 2 weeks |
| Beta-adrenergic blocking agents [e.g., timolol (Timoptic®, Betimol®, Timoptic XE®, Istatol®), timolol maleate and dorzolamide hydrochloride (Cosopt®), timolol maleate and brimonidine tartrate (Combigan®), levobunolol (Akbeta®, Betagan®), betaxolol (Betoptic®, Betopic-S®), metipranolol (Opti-Pranolol®), carteolol (Ocupress®)] | 4 weeks |
| Prostaglandin analogs (e.g., latanoprost (Xalatan®), travoprost (Travatan®), bimatoprost (Lumigan®), tafluprost (Zioptan™)] | 4 weeks |

3. Exclusion Criteria (the sponsor may add additional criteria)
    a. Females who are pregnant, breast feeding, or planning a pregnancy.
    b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
    c. Current, or past history of, severe hepatic or renal impairment.
    d. Current, or history within 2 months prior to baseline of, significant ocular disease, e.g., corneal edema, uveitis, ocular infection, or ocular trauma in either eye.
    e. Current corneal abnormalities that would prevent accurate IOP readings with the Goldmann applanation tonometer.
    f. Functionally significant visual field loss.
    g. Contraindication to latanoprost therapy or known hypersensitivity to any component of latanoprost therapy.
    h. Use at any time prior to baseline of an intraocular corticosteroid implant.
    i. Use within 1 week prior to baseline of contact lens.

j. Use within 2 weeks prior to baseline of: 1) topical ophthalmic corticosteroid, or 2) topical corticosteroid.
k. Use within 1 month prior to baseline of: 1) systemic corticosteroid or 2) high- dose salicylate therapy.
l. Use within 6 months prior to baseline of intravitreal or subtenon injection of ophthalmic corticosteroid.
m. Underwent within 6 months prior to baseline any other intraocular surgery (e.g., cataract surgery).
n. Underwent within 12 months prior to baseline refractive surgery, filtering surgery, or laser surgery for IOP reduction.

4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
   a. Ocular hypotensive drug product other than a study treatment, e.g., acetazolamide (Diamox®), betaxolol solution (Betoptic®), betaxolol and pilocarpine (Betoptic® Pilo), bimatoprost (Lumigan®), brimonidine tartrate (Alphagan®, Alphagan® P), brimonidine tartrate and brinzolamide (Simbrinza®), brimonidine tartrate and timolol maleate (Combigan®), brinzolamide (Azopt®), carbachol (Miostat®), carteolol (Ocupress®), dorzolamide hydrochloride (Trusopt®), dorzolamide hydrochloride and timolol maleate (Cosopt®), epinephrine (Epifrin®), latanoprost (Xalatan®), levobetaxolol (Betaxon®), levobunolol (Akbeta®, Betagan®), mannitol (Osmitrol®), metipranolol (OptiPranolol®), pilocarpine (Isopto® Carpine, Pilopine HS®), tafluprost (Zioptan™), timolol (Betimol®, Istalol®, Timoptic®, Timoptic XE®), travoprost (Travatan®, Travatan Z®).
   b. Ophthalmic over-the-counter or prescription product, other than study treatment and the occasional use of artificial tears.
   c. Oral carbonic anhydrase inhibitor.
   d. High-dose salicylate therapy.
   e. Topical or systemic corticosteroid.
   f. Topical ophthalmic corticosteroid.
   g. Intraocular corticosteroid implant.
   h. Intravitreal or subtenon injection of ophthalmic corticosteroid.
   i. Systemic beta-adrenergic blocking drug product.
   j. Change in concurrent treatment or initiation of treatment with agents potentially affecting IOP, e.g., antihypertensive medication.
   k. Contact lenses.
   l. Ocular surgery.

5. The recommended primary endpoint is the mean difference from baseline in IOP of both eyes between the 2 treatment groups at 4 time points, one at the Day 14 (Week 2) visit pre-dose then one 8 – 12 hours post-dose, and one at Day 42 (Week 6) visit pre-dose then one 8 – 12 hours post-dose.

6. The enrolled subjects should have mixture of light and dark colored irides similar in proportion to the U.S. population.

7. Subjects whose condition worsens (e.g., IOP ≥ 36 mm Hg in either eye) and require alternate or supplemental therapy for the treatment of their chronic open angle glaucoma or ocular hypertension during the study should be discontinued, excluded from the PP population analysis, and provided with effective treatment.

8. Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug (RLD). For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulations for ANDAs, 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

9. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Age
    e. Sex
    f. Race
    g. Iris color
    h. Name of planned treatment
    i. Name of actual treatment
    j. Safety population flag (yes/no)
    k. Reason for exclusion from safety population
    l. Intent-to-Treat (ITT) population flag (yes/no)
    m. Per Protocol (PP) population flag (yes/no)
    n. Reason for exclusion from PP population
    o. Completers population flag (yes/no)
    p. Randomized population flag (yes/no)
    q. Datetime of first exposure to treatment
    r. Datetime of last exposure to treatment
    s. End of study date
    t. End of study status
    u. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    v. Intraocular pressure (IOP) of both eyes at baseline (Day0/hour0)
    w. Best corrected visual acuity of both eyes at baseline, 20/200 or better (yes/no)
    x. Compliance rate (%)

y. Subject missed the scheduled application for more than 3 consecutive days (yes/no)
z. Adverse event(s) reported (yes/no)
aa. Concomitant medication (yes/no)

10. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier (if applicable)
    d. Name of planned treatment
    e. Name of actual treatment
    f. Safety population flag (yes/no)
    g. Intent-to-Treat (ITT) population flag (yes/no)
    h. Per-Protocol (PP) population flag (yes/no)
    i. Completers population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Analysis timepoint (e.g., Week 2, hour 0)
    n. Intraocular pressure (IOP) of both eyes
    o. Additional treatment required during the visit (yes/no)
    p. Adverse event reported during the visit (yes/no)
    q. Concomitant medication during the visit (yes/no)

11. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

12. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[1]

[1] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm