Contains Nonbinding Recommendations

Draft Guidance on Brimonidine Tartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Brimonidine tartrate

Dosage Form; Route: Solution/drops; ophthalmic

Strength: 0.1%

Recommended Studies: Two options: waiver or in vivo study

Additional comments: Brimonidine tartrate ophthalmic solution products should have comparable physicochemical properties to the Reference Standard (RS) including but not limited to pH, specific gravity, buffer capacity, osmolality, and viscosity, if applicable. Comparative analysis should be performed on three exhibit batches, if available, of both test and RS products.

I. Waiver option:

To qualify for a waiver of the in vivo bioequivalence (BE) study requirement, a generic brimonidine tartrate ophthalmic solution product must be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD).

An in vivo BE study with clinical endpoints is requested for any brimonidine tartrate ophthalmic solution product that has a different inactive ingredient from the RLD,[3] a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD, or differences in comparative physicochemical characterization data.

II. In Vivo option:

Recommended studies: One study

Type of study: BE study with clinical endpoint

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.
[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. *ANDA Submissions –Refuse-to-Receive Standards: Guidance for Industry.*
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm370352.pdf

Design: Randomized (1:1), double-masked, parallel, two-arm, in vivo
Strength: 0.1%
Subjects: Males and females with chronic open-angle glaucoma or ocular hypertension in both eyes.
Additional comments: Specific recommendations are provided below.

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

Bioequivalence based on (95% CI): Clinical endpoint (in vivo option)

Dissolution test method and sampling times: Not applicable

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs recommends conducting a BE study with a clinical endpoint in the treatment of open-angle glaucoma and ocular hypertension comparing the test product versus the RLD, each applied as one drop in both eyes three times daily at approximately 8:00, 16:00 and 22:00 for 42 days (6 weeks).

2. Inclusion Criteria (the sponsor 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, 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 $\geq$ 22 mm Hg and $\leq$ 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 two 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 brimonidine therapy or known hypersensitivity to any component of brimonidine therapy.
   h. Use at any time prior to baseline of intraocular corticosteroid implant.
   i. Use within one week prior to baseline of contact lens.
   j. Use within two weeks prior to baseline of: 1) topical ophthalmic corticosteroid, or 2) topical corticosteroid.
   k. Use within one month prior to baseline of: 1) systemic corticosteroid, 2) monoamine oxidase (MAO) inhibitor therapy, 3) any antidepressant which affects noradrenergic transmission (e.g., tricylic antidepressants, mianserin) or 4) adrenergic-augmenting psychotropic drug (e.g., desipramine, amitriptyline).
   l. Use within six months prior to baseline of intravitreal or subtenon injection of ophthalmic corticosteroid.
   m. Underwent within six months prior to baseline any other intraocular surgery (e.g., cataract surgery).
   n. Underwent within twelve 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 study treatment, e.g., acetazolamide (Diamox®), betaxolol (Betoptic®, Betopic-S®), betaxolol and pilocarpine (Betoptic® Pilo), bimatoprost (Lumigan®), 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. Monoamine oxidase (MAO) inhibitor.
    d. Tricyclic antidepressant or any other antidepressant which affects noradrenergic transmission.
    e. Adrenergic-augmenting psychotropic drug (e.g., desipramine, amitriptyline).
    f. Topical or systemic corticosteroid.
    g. Topical ophthalmic corticosteroid.
    h. Intraocular corticosteroid implant.
    i. Intravitreal or subtenon injection of ophthalmic corticosteroid.
    j. Systemic beta-adrenergic blocking drug product.
    k. Change in concurrent treatment or initiation of treatment with agents potentially affecting IOP, e.g., antihypertensive medication.
    l. Contact lenses.
    m. Ocular surgery.

5. The recommended primary endpoint is the mean difference in intraocular pressure (IOP) of both eyes between the two treatment groups at four time points, i.e., at approximately 8:00 (hour 0; before the morning drop) and 10:00 (hour 2) at the Day 14 (week 2) and Day 42 (week 6) visits.

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

7. The protocol should clearly define the per-protocol (PP) and safety populations.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, instill a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 3 consecutive days, and complete evaluations at Day 14 (week 2) and Day 42 (week 6) within the designated visit window (+/- 4 days) with no protocol violations

that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.

b. The safety population includes all randomized subjects who receive study product.

8. 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.

9. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

10. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

11. Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration as the 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 abbreviated new drug applications (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.

12. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

13. A detailed description of the masking procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate masking of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. If the two treatments differ in appearance, evaluators should not be in the room whenever the treatment is taken out of the external packaging or the subject is dosed with study treatment.

14. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time. Separate shipments sent to a clinical site should each have testing samples retained.

15. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

16. To establish bioequivalence, the limits of each two-sided 95% confidence interval of the treatment difference (test – reference) for mean IOP of both eyes (continuous variable) at all four follow-up points (i.e., at approximately 8:00 (hour 0; before the morning drop) and 10:00 (hour 2) at the Day 14 (week 2) and Day 42 (week 6) visits must be within ± 1.5 mm Hg using the PP population for all time points measured and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

17. The results of the primary endpoint at the four time points obtained by both the test product and RLD should be compared to the results that supported the approval of the RLD and any historical results in the literature.

18. Study data should be submitted in standardized format. Please refer to the study data standards published at www.FDA.gov[4].

19. 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)

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

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 applications for more than 3 consecutive days (yes/no)
z. Adverse event reported (yes/no)
aa. Concomitant medication (yes/no)

20. Please provide the basic data structure (BDS) dataset with records per subject, 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., hour 0, hour 2)
    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)

21. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of brimonidine tartrate.