Contains Nonbinding Recommendations

Draft Guidance on Betaxolol Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Betaxolol hydrochloride

Dosage Form; Route: Suspension/drops; ophthalmic

Recommended Studies: One study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized (1:1), double-masked, parallel, two-arm in vivo
Strength: EQ 0.25 % Base
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 (N/A)

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

Dissolution test method and sampling times: N/A

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 versus the reference listed drug (RLD), each applied as one drop in both eyes two times daily at approximately 8:00 a.m., and 8:00 p.m. 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 an appropriate washout period.
   c. Adequate washout 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.

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®, Betoptic-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, 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 betaxolol therapy or known hypersensitivity to any component of betaxolol therapy.
   h. Use at any time prior to baseline of an 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 or 2) high-dose salicylate therapy.

l. Use within six months prior to baseline of intravitreal or subtenon injection of ophthalmic corticosteroid.
m. Any other intraocular surgery within six months prior to baseline (e.g., cataract surgery).
n. Refractive surgery, filtering surgery, or laser surgery for IOP reduction within twelve months prior to baseline.

4. The protocol should include a list of the prescription and nonprescription/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 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 nonprescription/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 in IOP of both eyes between the two treatment groups at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a.m. (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 U.S. population.

7. The protocol should clearly define the per-protocol (PP) and safety populations.
   a. The accepted PP population used for BE 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 $\geq$ 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 dates 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 AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is needed to determine whether 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 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 and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). The FDA recommends 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. Applicants should provide a detailed description of the masking procedure 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 a study treatment.

14. 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 BE 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 and good clinical practices. 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.

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

16. To establish BE, 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 a.m. (hour 0; before the morning drop) and 10:00 a.m. (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 at least three 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 to the OGD in electronic format. All data should be submitted as a SAS .xpt file, created using SAS XPORT (not CPORT).
    a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = TEST and B = REFERENCE.

    b. Provide a separate data set for demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication, medical history, compliance, and comment variables.

19. Applicants should provide a summary data set containing a separate line listing for each subject, if data exist. Use the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)

f. Sex
g. Race
h. Iris color
i. Name of actual treatment (exposure): test product, RLD
j. Completed the study (yes/no)
k. Reason for premature discontinuation of subject
l. Subject required additional treatment for open-angle glaucoma or ocular hypertension due to unsatisfactory treatment response (yes/no)
m. Per Protocol (PP) population inclusion (yes/no)
n. Reason for exclusion from PP population
o. Safety population inclusion (yes/no)
p. Reason for exclusion from safety population
q. Mean IOP of both eyes at Day 0/hour 0
r. Mean IOP of both eyes at Day 0/hour 2
s. Mean IOP of both eyes at Day 14 (week 2)/hour 0
t. Mean IOP of both eyes at Day 14 (week 2)/hour 2
u. Mean IOP of both eyes at Day 42 (week 6)/hour 0
v. Mean IOP of both eyes at Day 42 (week 6)/hour 2
w. Treatment compliance: number of missed doses per subject
x. Concomitant medication (yes/no)
y. Adverse event(s) reported (yes/no)

Table 2 provides an example. Note: this sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary data set containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	iris_col	EXTRT	completd	disc_rs	add_trt	pp	pp_rs	safety	safe_rs
101	1	01	54	YEARS	F	1		A	Y		N	Y		Y	
101	2	01	58	YEARS	F	1		B	Y		N	Y		Y	

iop0_0	iop0_2	iop14_0	iop14_2	iop42_0	iop42_2	complian	CM	AE
						0	Y	Y
						0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID:	Study identifier
SUBJID:	Subject identifier for the study
SITEID:	Study site identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, M=male, F=female, U=unknown
RACE:	Race, 1=white, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or other Pacific Islanders
iris_col:	Iris color, e.g., BL-blue; BR=brown; GRA=gray; GRE=green, HA=hazel
EXTRT:	Name of actual treatment (exposure), e.g., A=test product, B= RLD
completd:	Subject completed the study, Y=yes, N=no
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unmasked, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for elevated intraocular pressure due to unsatisfactory treatment response, Y=yes, N=no
pp:	Per Protocol (PP) population inclusion, Y=yes, N=no
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
safety:	Safety population inclusion, Y=yes, N=no
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
iop0_0:	Mean intraocular pressure (IOP) of both eyes at Day 0/hour 0
iop0_2:	Mean IOP of both eyes at Day 0/hour 2
iop14_0:	Mean IOP of both eyes at Day 14 (week 2)/hour 0
iop14_2:	Mean IOP of both eyes at Day 14 (week 2)/hour 2
iop42_0:	Mean IOP of both eyes at Day 42 (week 6)/hour 0
iop42_2:	Mean IOP of both eyes at Day 42 (week 6)/hour 2
complian:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, Y=yes, N=no AE: Adverse event(s) reported, Y=yes, N=no

20. The study data should be submitted in standardized format. Consider the implementation and use of data standards as early as possible in the product development lifecycle, so that standards are accounted for in the design, conduct, and analysis of clinical studies. For more details, please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

21. The protocol should include a full, detailed statistical analysis plan and describe how missing data will be prevented and handled if the problem occurs.

22. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of betaxolol.