

## Draft Guidance on Alprostadil

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**Dosage Form; Route:** Suppository; urethral

**Recommended studies:** One study

1. Type of study: Clinical bioequivalence (BE) study with pharmacodynamic endpoint  
Design: Randomized, double-blind, parallel, three-arm, vehicle-controlled, in vivo  
Strengths: 0.125 mg, 0.25 mg, 0.5 mg, and 1 mg [**NOTE:** any dosage strength requested by an ANDA applicant for approval needs to be supported by the generation of adequate data for that particular dosage strength in a BE study with pharmacodynamic endpoint]  
Subjects: Males, aged 18 years or older, with erectile dysfunction.  
Addition comments: Specific recommendations are provided below

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

**Bioequivalence based on (90% CI):** Pharmacodynamic endpoint

**Waiver request of in vivo testing:** N/A

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

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

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with pharmacodynamic endpoint in the treatment of erectile dysfunction comparing the test product versus the reference listed drug (RLD) and vehicle control. Qualified subjects will be administered a maximum of nine doses of study treatment in the clinic. While dosing may begin with single doses of 0.125 mg, 0.25 mg or placebo, titration is required for the 0.5 mg and 1 mg doses. If the one dose of study treatment administered during the clinic visit did not result in an erection adequate for intercourse, recommend scheduling the next clinic visit in 1 to 5 days. This schedule will comply with the RLD labeling, which states that the maximum frequency of use is no more than two systems per 24-hour

period, i.e., the RLD labeling permits the administration of a single dose of alprostadil urethral suppository during an afternoon clinic appointment followed the next day by the administration of a single dose of alprostadil urethral suppository during a morning appointment.

2. The placebo control arm (vehicle of test product) is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
3. Treatment is administered for at most nine clinic visits, with the initial three visits at either the 0.125 mg or 0.25 mg strength. Titration for the next higher dosage strength occurs only if the previous dose fails to result in an adequate erection. Because the RLD labeling recommends that patients are to be titrated to the lowest dose that is adequate for sexual intercourse, the minimum number of clinic visits is three and the maximum is nine. Once an erection adequate for intercourse occurs, titration should stop. Test, reference, and placebo should be administered for the strength at which an adequate erection occurs. The following is an example of such a treatment allocation schedule:

SEQ	Visit1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
1	TEST 0.125mg	RLD 0.125mg	Placebo	RLD 0.25mg	Placebo	TEST 0.25mg	Placebo	TEST 0.5mg	RLD 0.5mg
2	TEST 0.125mg	Placebo	RLD 0.125mg	Placebo	RLD 0.25mg	TEST 0.25mg	RLD 0.5mg	TEST 0.5mg	Placebo
3	RLD 0.125mg	TEST 0.125mg	Placebo	TEST 0.25mg	Placebo	RLD 0.25mg	Placebo	RLD 0.5mg	TEST 0.5mg
4	TEST 0.25mg	RLD 0.25mg	Placebo	RLD 0.5mg	Placebo	TEST 0.500mg	Placebo	TEST 1mg	RLD 1mg
5	TEST 0.25mg	Placebo	RLD 0.25mg	Placebo	RLD 0.5mg	TEST 0.5mg	RLD 1mg	TEST 1mg	Placebo
6	RLD 0.25mg	TEST 0.25mg	Placebo	TEST 0.5mg	Placebo	RLD 0.5mg	Placebo	RLD 1mg	TEST 1mg
7	RLD 0.125mg	Placebo	TEST 0.125mg	Placebo	TEST 0.25mg	RLD 0.25mg	TEST 0.5mg	RLD 0.5mg	Placebo
8	Placebo	TEST 0.125mg	RLD 0.125mg	TEST 0.25mg	RLD 0.25mg	Placebo	RLD 0.5mg	Placebo	TEST 0.5mg
9	Placebo	RLD 0.125mg	TEST 0.125mg	RLD 0.25mg	TEST 0.25mg	Placebo	TEST 0.5mg	Placebo	RLD 0.5mg
10	RLD 0.25mg	Placebo	TEST 0.25mg	Placebo	TEST 0.5mg	RLD 0.5mg	TEST 1mg	RLD 1mg	Placebo
11	Placebo	TEST 0.25mg	RLD 0.25mg	TEST 0.5mg	RLD 0.5mg	Placebo	RLD 1mg	Placebo	TEST 1mg
12	Placebo	RLD 0.25mg	TEST 0.25mg	RLD 0.5mg	TEST 0.5mg	Placebo	TEST 1mg	Placebo	RLD 1mg

4. Inclusion criteria (the sponsor may add additional criteria):
  - a. Male aged  $\geq 18$  years with erectile dysfunction.

- b. Inability, when not using any device(s) or drug product(s) for the treatment of erectile dysfunction, to achieve or maintain an erection adequate for intercourse during the three months prior to study entry.
  - c. Willing to discontinue use two weeks prior to enrollment of any treatment for erectile dysfunction (e.g., PDE5 inhibitors, vacuum pump, band therapy, intracavernosal injections).
5. Exclusion criteria (the sponsor may add additional criteria):
- a. Female.
  - b. Prior exposure to alprostadil (e.g., alprostadil urethral suppository, alprostadil cream, or alprostadil injection).
  - c. Known allergy or hypersensitivity reaction to alprostadil or any of the study treatment excipients
  - d. Sickle-cell or other disease interfering with study drug administration or trial participation.
  - e. Myocardial infarction within previous six months and history of heart failure or unstable angina.
  - f. Poorly controlled diabetes mellitus.
  - g. Active vasculitis.
  - h. Untreated primary or secondary hypogonadism.
  - i. Life expectancy less than six months
  - j. Waking erections adequate for vaginal penetration within previous three months.
  - k. Indwelling catheter.
  - l. Abnormal penile anatomy, penile implant, or poor hygiene.
  - m. Clinically significant anterior urethral stricture, meatal stenosis, or active urinary tract infection.
  - n. History of Peyronie's disease
6. The protocol should include a list of the prescription and nonprescription/over-the-counter drug products that are prohibited during the study, such as:
- a. Alprostadil-containing product, except for study medication.
  - b. Device(s) for the treatment of erectile dysfunction
  - c. Drug product(s) for the treatment of erectile dysfunction
7. The recommended primary endpoint is erectile response during in-office titration where 0 = "failure," defined as an erection inadequate for intercourse, or 1 = "success," defined as the subject achieving an erection adequate for intercourse during in-office titration.
8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT), and safety populations.
- a. The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, received at least one assigned study treatment, and did not have any protocol violations that would affect the treatment evaluation.
  - b. The mITT population includes all randomized subjects who meet all inclusion/exclusion criteria and received at least one assigned study treatment.

- c. The safety population includes all randomized subjects who received at least one study treatment.
9. Subjects who discontinued early from the study for any reason after receiving at least one assigned study treatment should be included in the PP and mITT populations.
10. 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.
11. 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.
12. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then the sponsor must clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, and/or systemic or local availability of the drug.
13. 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). 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.
14. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and vehicle-control products should be similar in appearance to make differences in treatment less obvious to the subjects and examiners, and to maintain adequate blinding of evaluators. Neither the subject nor the investigator should be able to identify the treatment.
15. 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. Refer to 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 (GLPs) and good clinical practices (GCPs). 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.

16. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.
17. To establish bioequivalence, it is recommended the following compound hypotheses be tested using the PP population:

$$H_0: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$

where  $\pi_T$  = the success rate of the primary endpoint for the treatment group, and  $\pi_R$  = the success rate of the primary endpoint for the reference group.

The null hypothesis,  $H_0$ , is rejected with a type I error ( $\alpha$ ) of 0.05 (two one-sided tests) if the 90% confidence interval for the difference of the success rates between test and reference products ( $\pi_T - \pi_R$ ) is contained within the interval  $[\Delta_1, \Delta_2]$ , where  $\Delta_1 = -0.20$  and  $\Delta_2 = 0.20$ . Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

18. To establish sensitivity for each dosage strength, the test and reference products should both be statistically superior to the placebo. Conduct a separate appropriate inferential test for each dosage strength with a type I error ( $\alpha$ ) of 0.05, using the mITT population and the primary endpoint.
19. 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).
- 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 = RLD and B = TEST).
  - 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.
20. Provide a summary data set containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- Study identifier
  - Subject identifier
  - Site identifier: study center
  - Age
  - Age units (years)
  - Sex (all subjects should be male)
  - Race
  - Name of actual treatment (exposure) at visit 1: test product 0.125 mg, RLD 0.125 mg, vehicle control, none, test product 0.25 mg, RLD 0.25 mg, etc.
  - Name of actual treatment (exposure) at visit 2: test product 0.125 mg, RLD 0.125 mg, vehicle control, none, test product 0.25 mg, RLD 0.25 mg, etc.

- j. Name of actual treatment (exposure) at visit 3: test product 0.125 mg, RLD 0.125 mg, vehicle control, none, test product 0.25 mg, RLD 0.25 mg, etc.
- k. Name of actual treatment (exposure) at visit 4: test product 0.25 mg, RLD 0.25 mg, vehicle control, none, test product 0.500 mg, RLD 0.500 mg, etc.
- l. Name of actual treatment (exposure) at visit 5: test product 0.25 mg, RLD 0.25 mg, vehicle control, none, test product 0.500 mg, RLD 0.500 mg, etc.
- m. Name of actual treatment (exposure) at visit 6: test product 0.25 mg, RLD 0.25 mg, vehicle control, none, test product 0.5 mg, RLD 0.5 mg, etc.
- n. Name of actual treatment (exposure) at visit 7: test product 0.5 mg, RLD 0.5 mg, vehicle control, none, test product 1 mg, RLD 1 mg, etc.
- o. Name of actual treatment (exposure) at visit 8: test product 0.5 mg, RLD 0.5 mg, vehicle control, none, test product 1 mg, RLD 1 mg, etc.
- p. Name of actual treatment (exposure) at visit 9: test product 0.5 mg, RLD 0.5 mg, vehicle control, none, test product 1 mg, RLD 1 mg, etc.
- q. Total number of treatments (none, one, two, three, ..., nine)
- r. Completed the study (yes/no)
- s. Reason for premature discontinuation of subject
- t. PP population inclusion (yes/no)
- u. Reason for exclusion from PP population
- v. Modified Intent to Treat (mITT) population inclusion (yes/no)
- w. Reason for exclusion from mITT population
- x. Safety population inclusion (yes/no)
- y. Reason for exclusion from safety population
- z. Erectile response at visit 1
- aa. Erectile response at visit 2
- bb. Erectile response at visit 3
- cc. Erectile response at visit 4
- dd. Erectile response at visit 5
- ee. Erectile response at visit 6
- ff. Erectile response at visit 7
- gg. Erectile response at visit 8
- hh. Erectile response at visit 9
- ii. Concomitant medication (yes/no)
- jj. Adverse event(s) reported (yes/no)

Refer to Table 1 as an example.

**Table 1: Example of a summary data set containing one line listing for each subject**

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT_1	EXTRT_2	EXTRT_3	EXTRT_4	...	EXTRT_9	num_irt	completed	disc_rr	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	visit_1	visit_2	visit_3	visit_4	...	visit_9	CM	AE
101	1	01	52	YEARS	M	1	B	C	A	D		C	6	Y		Y		Y		Y		0	0	0	0		1	Y	Y
101	2	01	55	YEARS	M	1	C	A	B	E		D	6	Y		Y		Y		Y		1	1	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, e.g., 1=white, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or other Pacific Islanders
- EXTRT\_1: Name of actual treatment (exposure) administered at visit 1, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_2: Name of actual treatment (exposure) administered at visit 2, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_3: Name of actual treatment (exposure) administered at visit 3, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_4: Name of actual treatment (exposure) administered at visit 4, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_5: Name of actual treatment (exposure) administered at visit 5, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_6: Name of actual treatment (exposure) administered at visit 6, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_7: Name of actual treatment (exposure) administered at visit 7, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
- EXTRT\_8: Name of actual treatment (exposure) administered at visit 8, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.

EXTRT_9:	Name of actual treatment (exposure) administered at visit 9, e.g., A=test product 0.125 mg, B= RLD 0.125 mg, C=vehicle control, 0=no treatment administered, D=test product 0.25 mg, E=RLD 0.25 mg, etc.
num_trt:	Total number of treatments administered (e.g., 0=none, 1=one)
completed:	Completed the study, Y=yes, N=no
disc_rr:	Reason for premature discontinuation of subject, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
pp:	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.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, B=negative baseline culture, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
visit_1:	Erectile response at visit 1, e.g., 0= failure or 1=success
visit_2:	Erectile response at visit 2, e.g., 0= failure or 1=success
visit_3:	Erectile response at visit 3, e.g., 0= failure or 1=success
visit_4:	Erectile response at visit 4, e.g., 0= failure or 1=success
visit_5:	Erectile response at visit 5, e.g., 0= failure or 1=success
visit_6:	Erectile response at visit 6, e.g., 0= failure or 1=success
visit_7:	Erectile response at visit 7, e.g., 0= failure or 1=success
visit_8:	Erectile response at visit 8, e.g., 0= failure or 1=success
visit_9:	Erectile response at visit 9, e.g., 0= failure or 1=success
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

21. 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 data standards are accounted for in the design, conduct, and analysis stages of clinical studies. For more details, please refer to <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.
22. The protocol should include a full detailed statistical analysis plan and describe how missing data will be prevented and handled if it exists.
23. 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 alprostadil.