Contains Nonbinding Recommendations

Draft Guidance on Dinoprostone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Dinoprostone

Form/Route: Suppository; Vaginal

Recommended study: 1 study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized, double-blind, parallel, 2-arm, in vivo
Strength: 20mg
Subjects: Pregnant female subject aged at least 18 years. Subject undergoing a termination of pregnancy from the 12th through the 20th gestation weeks as calculated from the first day of the last normal menstrual period AND/OR undergoing evacuation of the uterine contents in the management of missed abortion or intrauterine fetal death up to 28 weeks of gestational age as calculated from the first day of the last normal menstrual period AND/OR undergoing evacuation of uterine contents in the management of nonmetastatic gestational trophoblastic disease (benign hydatiform mole).
Additional comments: Specific recommendations are provided below.

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

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times:
Please note that a **Dissolution Method Database** is available to the public at the Office of Generic Drug (OGD) website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please 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 application.

Additional comments regarding the BE study with a clinical endpoint:

1) The OGD recommends a BE study with a clinical endpoint comparing the dinoprostone vaginal suppository 20 mg test product versus the reference listed drug (RLD), with each subject receiving one suppository inserted high into the vagina, the subject remaining in the supine position for ten minutes following insertion, and additional intravaginal administration of each subsequent suppository at 3- to 5-hour intervals until 48-hours after the first insertion OR evacuation of uterine contents occurs. The primary endpoint evaluation occurs at 48-hours after the first insertion of the assigned product OR when evacuation of uterine contents occurs, if prior to the 48-hour time point.

2) The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population identified as "treatment success" occurring during the 48-hours after the first insertion of the assigned product. A "treatment success" is defined as evacuation of uterine contents (complete or incomplete) at any time during the 48-hours after the first insertion of the assigned product. A subject undergoing additional measures following an incomplete evacuation of uterine contents (e.g., suction curettage or dilation and curettage) would still be considered to be a "treatment success".

3) Recommend that if no evacuation of uterine contents has occurred by the 48-hour timepoint, the investigator will determine the appropriate management of the subject.

4) Inclusion Criteria:
   a. Pregnant female subject aged at least 18 years.
   b. Subject undergoing a termination of pregnancy from the 12^{th} through the 20^{th} gestation weeks as calculated from the first day of the last normal menstrual period AND/OR undergoing evacuation of the uterine contents in the management of missed abortion or intrauterine fetal death up to 28 weeks of gestational age as calculated from the first day of the last normal menstrual period AND/OR undergoing evacuation of uterine contents in the management of nonmetastatic gestational trophoblastic disease (benign hydatiform mole)]. If the sponsor opts to enroll subjects with different treatment indications, the subjects with each indication should be stratified, in order that an approximately equal number of patients with each indication are represented in each of the two arms.
   c. When a pregnancy diagnosed as missed abortion is electively interrupted with intravaginal administration of dinoprostone, confirmation of intrauterine fetal death should be obtained in respect to a negative pregnancy test for chorionic gonadotropic activity (U.C.G. test or equivalent) or by ultrasound.
   d. When a pregnancy with late fetal intrauterine death is interrupted with intravaginal administration of dinoprostone, confirmation of intrauterine fetal death by ultrasound should be obtained prior to treatment.

5) Stratify treatment groups by parity (i.e., nulliparous versus multiparous) to ensure that similar proportions of nulliparous and multiparous women are in each of the two treatment groups. If the sponsor opts to enroll subjects with different treatment indications, the treatment groups should also be stratified by treatment indication to ensure that similar proportions of women with each of the three possible indications are in each of the two treatment groups.

6) Exclusion Criteria:
   a. Live fetus in utero has reached the stage of viability.
   b. Active uterine pains or rupture of the membranes.
   c. Acute pelvic inflammatory disease.
   d. Subjects with active cardiac, pulmonary, renal, or hepatic disease.
   e. Subjects with a history of asthma, diabetes, epilepsy, hysterotomy or Caesarian section.
   f. Subject with known hypersensitivity to dinoprostone.
   g. Previous failed attempt to terminate the present pregnancy.

7) Dinoprostone, as with other potent oxytocic agents, should be used only with strict adherence to recommended dosages. Dinoprostone should be used by medically trained personnel in a hospital which can provide immediate intensive care and acute surgical facilities.

8) Dinoprostone does not appear to directly affect the fetoplacental unit. Therefore, the possibility does exist that the previable fetus aborted by dinoprostone could exhibit transient life signs. Dinoprostone should not be considered a feticidal agent.

9) Evidence from animal studies had suggested that certain prostaglandins may have some teratogenic potential. Therefore, any failed pregnancy termination with dinoprostone should be completed by some other means.

10) As in spontaneous abortion, where the process is sometimes incomplete, abortion induced by Dinoprostone vaginal suppositories, 20 mg may sometimes be incomplete. In such cases, other measures should be taken to assure complete abortion.

11) The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Concomitant use with other oxytocic agents.

12) 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 met all inclusion/exclusion criteria, had no protocol violations that would affect the treatment evaluation, who received a dose of the assigned product inserted at 3- to 5-hour intervals until abortion occurred OR until 48 hours after first assigned product insertion. The protocol should specify how compliance will be verified, e.g., data collected on case report form for date and time of all assigned product insertions, date and time of evacuation of uterine contents, and date and time of any additional measures to assure complete evacuation of uterine contents.
    b. The safety population includes all randomized subjects who received at least one dose of study product.

13) Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population as treatment failures (i.e., non-responders). Subjects discontinued early for other reasons should be excluded from the PP population.

14) Treatment groups should also be compared with regard to the mean time from first insertion of vaginal suppository to evacuation of uterine contents (partial or complete).

15) 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.

16) 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.

17) If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to 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.

18) 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.

19) A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

20) 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 21 CFR 58 and 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.

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

22) To establish bioequivalence, the 90% confidence interval of the difference in the "treatment success" rate between the test product and RLD treatment groups occurring during the 48-hour time period after the insertion of the assigned product must be within [-0.20, +0.20] for the dichotomous primary endpoint, using the PP study population.

23) The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

    <u>Equivalence Analysis</u>

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$

    versus

    H_A: $-.20 \leq p_T - p_R \leq .20$

    where p_T = success rate of test treatment p_R = success rate of reference treatment.

    Let

n_T = sample size of test treatment group

cn_T = number of subjects with success in test treatment group

n_R = sample size of reference treatment group

cn_R = number of subjects with success in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}.$$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645 \text{ se} - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645 \text{ se} + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -.20$ and $U \leq .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

24) The results of the primary endpoint 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.

25) Study data should be submitted to the OGD in electronic format.
   a. A list of file names, with a simple description of the content of each file, should be included.
   b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
   c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
   d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
   e. Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline Bishop Score, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

26) Please provide a summary dataset containing a separate line listing for each subject (if data exist) using 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. Name of Actual Treatment (exposure): test product, RLD, placebo
i. First Insertion of Assigned Treatment Date
j. First Insertion of Assigned Treatment Time
k. Last Insertion of Assigned Treatment Date
l. Last Insertion of Assigned Treatment Time
m. Total Number of Assigned Treatment Insertions
n. Duration of Treatment (total exposure in hours)
o. Per Protocol (PP) population inclusion (yes/no)
p. Reason for exclusion from PP population
q. Safety population inclusion (yes/no)
r. Reason for exclusion from safety population
s. Final designation as treatment success/treatment failure (yes/no)
t. Date of evacuation of uterine contents (complete or incomplete)
u. Time of evacuation of uterine contents (complete or incomplete)
v. Additional measures performed to ensure complete evacuation of uterine contents (yes/no)
w. Treatment compliance (yes/no)
x. Concomitant medication (yes/no)
y. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. 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 1: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	trt_fird	trt_firt	trt_lstd	trt_lstt	trt_num	EXDUR
101	001	01	20	YEARS	F	1	A	04/16/11	8:00	04/17/11	5:15	6	21.25
101	002	01	24	YEARS	F	1	B	04/17/11	9:15	04/17/11	21:15	3	12

pp	pp_rs	safety	safe_rs	trt_suc	evac_d	evac_t	add_meas	complian	CM	AE
Y		Y		Y	04/17/11	6:00	N	Y	Y	N
Y		Y		Y	04/17/11	22:00	N	Y	N	Y

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, e.g., 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:	Name of Actual Treatment (exposure), e.g. A=test product, B= RLD
trt_fird:	First Insertion of Assigned Treatment Date, e.g., month/date/year
trt_firt:	First Insertion of Assigned Treatment Time, e.g., 24-hour clock
trt_lstd:	Last Insertion of Assigned Treatment Date, e.g., month/date/year
trt_lstt:	Last Insertion of Assigned Treatment Time, e.g., 24-hour clock
trt_num:	Total Number of Assigned Treatment Insertions, e.g., 0 to 16
EXDUR:	Duration of Treatment (total time in hours from first insertion to last)
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=noncompliant, 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.
trt_suc:	Final designation, e.g., Y=Yes (treatment success), N=No (treatment failure)
evac_d:	Date of evacuation of uterine contents (complete or incomplete), e.g., month/date/year
evac_t:	Time of evacuation of uterine contents (complete or incomplete), e.g., 24-hour clock
add_meas:	Additional measures performed to ensure complete evacuation of uterine contents, e.g., Y=Yes, N=No
complian:	Treatment compliance (insert in vagina for at least 11 hours and no more than 13 hours), e.g., Y=Yes, N=No
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

27) 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 Dinoprostone.