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Draft Guidance on Dinoprostone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Insert, Extended Release; Vaginal

Recommended study: 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 10 mg (single dose: 1x10 mg for 12 hours)
Subjects: Pregnant female patients at or near term with a medical or obstetrical indication for the induction of labor.
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.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in 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 extended release vaginal insert 10 mg test product versus the reference listed drug (RLD) and placebo control, with each subject receiving one insert intravaginally for 12 hours and the primary endpoint evaluation occurring during the 12-hour observation period after the insertion of the assigned product.
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 12-hour observation period after the insertion of the assigned product. A “treatment success” is defined as attainment of an

increase of at least 3 in a Bishop score during the 12-hour observation period, the attainment of a Bishop score of ≥ 6 during the 12-hour observation period, or vaginal delivery occurring during the 12-hour observation period. It is recommended that the same individual perform the Bishop Score assessment at baseline, 6 hours after insertion and 12 hours after insertion.

3) Inclusion Criteria:
   a. Pregnant women aged ≥ 18 years.
   b. Medical or obstetrical indication for induction.
   c. Singleton pregnancy at ≥ 37 weeks gestation
   d. Cephalic presentation.
   e. Parity ≤ 3.
   f. Fetal reactive non-stress test.
   g. Bishop score ≤ 4 on admission.

Bishop score[1]				
Parameter\Score	**0**	**1**	**2**	**3**
Dilation	0 cm	1-2 cm	3-4 cm	5-6 cm
Effacement	0-30%	40-50%	60-70%	≥80%
Fetal Station	-3	-2	-1 to 0	+1 to +2
Consistency	Firm	Medium	Soft	-
Position	Posterior	Mid.	Anterior	-

4) Stratify treatment groups by parity (i.e., nulliparous versus multiparous) to ensure similar proportions of nulliparous and multiparous women in each of the three treatment groups.

5) Exclusion Criteria:
   a. Subject with known hypersensitivity to prostaglandins or constituent of the insert.
   b. Subject in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate, such as:
      - cases with a history of cesarean section or major uterine surgery
      - cases in which there is evidence or strong suspicion of marked cephalopelvic disproportion
      - cases in which there is a history of difficult labor and/or traumatic delivery
      - non-vertex presentation
      - cases with hyperactive or hypertonic uterine patterns
      - cases of clinical suspicion or definite evidence of fetal distress where delivery is not imminent
      - in obstetric emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention
   c. Subject with placenta previa or unexplained vaginal bleeding during this pregnancy.
   d. Subject for whom vaginal delivery is not indicated, such as vasa previa or active herpes genitalia.
   e. Prior attempts at cervical softening or induction of labor in the present pregnancy
   f. Subject already receiving intravenous oxytocic drugs.
   g. Premature rupture of membranes more than 4 hours prior to administration of the assigned product.
   h. History of asthma, glaucoma, or raised intraocular pressure.
   i. History of previous uterine hypertonicity.
   j. Spontaneous labor.
   k. Fetal death in-utero.

[1] Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol*. 1964 Aug; 24 (2): 266-8.

l. Use of aspirin, non-steroidal anti-inflammatory drugs or acetaminophen within 4 hours prior to administration of the assigned product.

6) Vaginal irritation should be evaluated at baseline and when the insert is removed and compared between treatment groups The protocol could use a scoring system and pre-specify definitions for various degrees of vaginal irritation.

7) The protocol should clearly define the per-protocol (PP), intent-to-treat (ITT) 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 single dose of the assigned product AND the assigned product was inserted for at least 11 hours with the final evaluation completed within the designated time window OR vaginal delivery occurred prior to 12 hours after assigned product insertion. The protocol should specify how compliance will be verified, e.g., data collected on case report form for assigned product insertion date and time, assigned product removal date and time, delivery method (i.e., vaginal delivery, Cesarean section) and delivery date and time.
   b. The ITT population includes all subjects who are randomized, receive the single dose of assigned product, and undergo at least one Bishop score assessment after insertion of assigned product.
   c. The safety population includes all randomized subjects who received study product.

8) 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, but included in the ITT population, using LOCF.

9) Treatment groups should also be compared with regard to the number of subjects with hypertonicity, fetal distress, and other potentially treatment-related obstetrical adverse events and events leading to early removal of the treatment insert.

10) Delivery mode (i.e., vaginal delivery, Cesarean section) and delivery date and time should be recorded for each subject and compared between treatment groups.

11) 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.

12) 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.

13) 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.

14) 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.

15) 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.

16) 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.

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

18) 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 12-hour observation 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.

19) As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p<0.05$) with regard to the "treatment success" rate occurring during the 12-hour observation period after the insertion of the assigned product, using the intent-to-treat (ITT) study population and Last Observation Carried Forward (LOCF).

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

Equivalence Analysis

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.

21) 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.

22) 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. Assigned Treatment Insertion Date

j. Assigned Treatment Insertion Time
k. Assigned Treatment Removal Date
l. Assigned Treatment Removal Time
m. Duration of Treatment (total exposure in hours)
n. Per Protocol (PP) population inclusion (yes/no)
o. Reason for exclusion from PP population
p. Intent to Treat (ITT) population inclusion (yes/no)
q. Reason for exclusion from ITT population
r. Safety population inclusion (yes/no)
s. Reason for exclusion from safety population
t. Bishop Score at baseline
u. Bishop Score at 6 hours after insertion
v. Bishop Score at 12 hours after insertion
w. Bishop Score increased by ≥ 3 points within 12 hours after insertion (yes/no)
x. Bishop Score increased to ≥ 6 within 12 hours after insertion (yes/no)
y. Method of Delivery (vaginal delivery/Cesarean section)
z. Delivery Date
aa. Delivery Time
bb. Vaginal Delivery occurred within 12 hours after insertion (yes/no)
cc. Final designation as treatment success/treatment failure (yes/no)
dd. Vaginal Irritation at baseline
ee. Vaginal Irritation at 12 hours after insertion
ff. Treatment compliance (yes/no)
gg. Concomitant medication (yes/no)
hh. 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_in_d	trt_in_t	trt_outd	trt_outt	EXDUR	pp	pp_rs	itt	itt_rs
101	001	01	20	YEARS	F	1	A	04/16/11	8:00	04/16/11	20:02	12	Y		Y	
101	002	01	24	YEARS	F	1	B	04/17/11	9:15	04/17/11	21:15	12	Y		Y	

safety	safe_rs	bish_b	bish_6	bish_12	bish_≥3	bish_≥6	deliv_m	deliv_d	deliv_t	vag_d_12	trt_suc	irr_b	irr_12	complian	CM	AE
Y		4	5	6	N	Y	V	04/17/11	7:05	Y	Y	0	1	Y	Y	N
Y		3	5	7	Y	Y	C	04/18/11	6:10	Y	Y	0	2	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, C=placebo
trt_in_d:	Assigned Treatment Insertion Date, e.g., month/date/year
trt_in_t:	Assigned Treatment Insertion Time, e.g., 24-hour clock
trt_outd:	Assigned Treatment Removal Date, e.g., month/date/year
trt_outt:	Assigned Treatment Removal Time, e.g., 24-hour clock
EXDUR:	Duration of Treatment (total exposure in hours)
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=insert fell out prior to 12 hours after insertion, C=noncompliant, etc.
itt:	Intent to Treat (ITT) population inclusion, e.g., Y=Yes, N=No
itt_rs:	Reason for exclusion from ITT population, e.g., A=never treated 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.
bish_b:	Bishop Score at baseline, e.g., integer ranging from 0 to 13
bish_6:	Bishop Score at 6 hours after insertion, e.g., integer ranging from 0 to 13
bish_12:	Bishop Score at 12 hours after insertion, e.g., integer ranging from 0 to 13
bish_≥3:	Bishop Score increased by ≥ 3 points within 12 hours after insertion, e.g., Y=Yes, N=No
bish_≥6:	Bishop Score increased to ≥ 6 within 12 hours after insertion, e.g., Y=Yes, N=No
deliv_m:	Delivery Method, e.g., V=vaginal delivery, C=Cesarean section
deliv_d:	Delivery Date (e.g., month/date/year)
deliv_t:	Delivery Time (e.g., 24-hour clock)
vag_d_12:	Vaginal Delivery occurred within 12 hours after insertion, e.g., Y=Yes, N=No
trt_suc:	Final designation, e.g., Y=Yes (treatment success), N=No (treatment failure)
irr_b:	Vaginal Irritation at baseline, e.g., 0=none; 1=minimal; 2=moderate; 3=severe
irr_12:	Vaginal Irritation at 12 hours after insertion, e.g., 0=none; 1=minimal; 2=moderate; 3=severe
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

23) 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.