Contains Nonbinding Recommendations

Draft Guidance on Diclofenac Epolamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Patch; topical

Recommended Studies: Four studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1.3%
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:

   - In this document, this dosage form is referred to as a topical delivery system (TDS) and includes products that may be described elsewhere or known as *patches*.
   - Unless otherwise justified, the diclofenac epolamine TDS should be applied to the same anatomical site on all subjects and worn for 12 hours. Applicants should randomize subjects to receive either the test or reference listed drug (RLD) product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body. A sampling time at 24-hour post-dose should be included in the BE study.
   - Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the PK may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.
   - The applicant should follow FDA's current thinking in the guidance "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" for the design and conduct of the PK BE study.

   Analytes to measure (in appropriate biological fluid): Diclofenac in plasma

   Bioequivalence based on (90% CI): Diclofenac

Waiver request of in vivo testing: Not applicable

NOTE: The strength of this topical dosage form is based upon the amount of drug in the TDS, expressed as a percentage based upon weight. A pharmaceutically equivalent drug product submitted in an ANDA should contain the same percentage of drug in the TDS, based upon weight.

The topical bioavailability of the drug from this drug product is influenced by the active surface area of the TDS. A drug product submitted in an ANDA should have the same active surface area as the RLD product.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of the test and RLD products. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: http://www.accessdata.fda.gov/scripts/cder/dissolution/.

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2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1.3%
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- The applicant may elect to evaluate the PK BE (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the BE, and independently, the comparative assessment of adhesion.
- The applicant should follow FDA's current thinking in the guidance "Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs" for the design and conduct of the independent adhesion study or the combined study to evaluate both PK BE and adhesion.

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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 1.3% (Dose: one-fourth of a 1.3% TDS)
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., one-fourth of the test product[1], one-fourth of the RLD product, optional vehicle TDS[2] and optional negative control[3]) should be applied

[1] The test product evaluated should be the actual TDS to be marketed.

simultaneously to each subject at different positions on an application site recommended in the approved labeling for the RLD product.

- Sequential TDS applications should be made to the same application site every 24 hours for a total of 21 consecutive days.
- There is insufficient information to determine whether it is safe to simultaneously apply two whole, diclofenac epolamine 1.3% TDS on the same subject during a 21-day skin irritation and sensitization study. Since the RLD product has a matrix design that can be safely cut, one-fourth of the RLD product can be used for these studies. If the test product also has a design that can be safely cut to a smaller size, it should also be cut, and one-fourth of the test product may be applied simultaneously with one-fourth of a RLD product (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test TDS in order to use a smaller TDS in this study. If the test TDS has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes study design different than what is recommended above, the prospective applicant may submit a pre-ANDA meeting request to discuss the proposed approach.
- The applicant should follow FDA's current thinking in the guidance "Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs" for the design and conduct of the skin irritation and sensitization study.

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4. Type of study: BE with clinical endpoint
   Design: Randomized, double-blind, parallel controlled, in vivo
   Strength: 1.3%
   Subjects: Males and non-pregnant, non-lactating females with ankle sprain
   Additional comments: Specific recommendations are provided below:

   - The OGD recommends conducting a BE study with a clinical endpoint in the treatment of acute ankle pain due to a minor ankle sprain. Subjects should be randomized to receive a diclofenac epolamine test product, the RLD product, or placebo control applied as one whole TDS every 12 hours for 3 days (i.e., total of 6 TDS) to the most painful area of the ankle. The primary endpoint is the change from baseline to 72 hours after application of the first TDS in the self-evaluation of pain on active mobilization measured in mm on the Visual Analog Scale (VAS).
   - Inclusion Criteria (the applicant may add additional criteria)
     a. Males and non-pregnant, non-lactating females aged 18 to 65 years with a minor ankle sprain that occurred within 48 hours of beginning the treatment phase AND

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[2] The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredient.
[3] An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.
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baseline self-evaluation of acute ankle pain on active mobilization by the VAS ≥ 50 mm.

- Exclusion Criteria (the applicant may add additional criteria)
  a. Pregnant or lactating female.
  b. Sprain occurred > 48 hours prior to study enrollment.
  c. Ankle sprain requires an orthopedic or surgical treatment.
  d. Ankle sprain treated prior to study entry by topical, oral, or parenteral NSAID, physiotherapy, ultrasound, physical therapy or acupuncture.
  e. Baseline self-evaluation of pain on active mobilization by the VAS < 50 mm.
  f. Non-intact or damaged skin within the area to be treated, e.g., eczema, psoriasis, exudative dermatitis, infected lesion, burn or wound.
  g. Medical history of asthma, urticaria, angioedema, bronchospasm, ulcer disease, gastrointestinal bleeding, coagulation defects, hypertension, edema, heart failure or cardiovascular disease.
  h. Medical history of any chronic pain disorder.
  i. Severe cardiac, renal or hepatic impairment.
  j. Severe systemic disease (e.g., cancer, severe acute infection)
  k. Use within one month prior to randomization of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral or parenteral corticosteroids or 4) cytotoxic drugs.
  l. Use within 7 days prior to randomization of any topical agent on the affected ankle.
  m. Use within 7 days prior to randomization of topical, oral or parenteral treatment with NSAIDs or aspirin.
  n. Use within 12 hours prior to randomization of an analgesic.
  o. Known allergy or hypersensitivity to diclofenac, aspirin or other NSAIDs, or any excipient in the test product or RLD.
- 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. Any therapy for treatment of pain, e.g., oral, topical, or parenteral NSAIDs, aspirin or narcotic pain medication, other than study treatment.
  b. Anticoagulants, lithium, digoxin, antidiabetic agents, quinolone antimicrobials, diuretics, ACE inhibitors, immunomodulators or immunosuppressive therapies, interferon, oral, systemic or topical corticosteroids, or cytotoxic drugs.

c. Topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, and powders) applied on or near the treatment area.

d. Treatment to the affected ankle, e.g., physiotherapy, ultrasound, physical therapy or acupuncture.

e. Subjects should be advised to avoid exposing the TDS application site(s) to external sources of direct heat, e.g., heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight, while wearing the TDS.

- The recommended primary endpoint of the study is the mean change from baseline to study day 3 (i.e., 72 hours after the first TDS application) in the self-evaluation of pain on active mobilization by the Visual Analog Scale (VAS) in mm.
- Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching should be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.
- Adhesion data should be collected during the course of the study to document that adhesion of the products is adequate. Applicants may consider establishing criteria for using tape to reinforce any TDS that are lifting during the study.
- The applicant should consider FDA's current thinking in the guidance "Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs" regarding the adhesion scale used to monitor TDS adhesion during the study.
- The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.

  a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
     i. Meet all inclusion/exclusion criteria
     ii. Are dosed a pre-specified proportion of the scheduled doses (Generally At least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., by the use of subject diaries).
     iii. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
     iv. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
  b. The mITT and safety populations include all randomized subjects who use at least one dose of product.

- Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward

(LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

- The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.
- If the study allows for the use of a rescue medication, the applicant should submit a data set that includes the date and time of each rescue medication use for each subject who used the rescue medication at any point during the study. The applicant should pre-specify rescue medication use (name, type, frequency, reason to use), maximum allowable amount of daily rescue medication use, and any limitations (e.g. cannot use rescue medication within pre-specified number of hours prior to primary endpoint evaluation) for rescue medication use during the study.
- 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.
- All pregnancies should be reported, including outcome information.
- If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).
- The method of randomization should be described in the protocol and the randomization schedule should be provided. 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 Applicant 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.
- A detailed description of the blinding procedure should 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.

- Applicants should 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 for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.
- It is the applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
- A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter that the study is sufficiently sensitive to detect differences between products.
- To establish bioequivalence for a continuous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

  $H_O: \mu_T/\mu_R < \theta_1$ or $\mu_T/\mu_R > \theta_2$ versus $H_A: \theta_1 \leq \mu_T/\mu_R \leq \theta_2$

  where μ_T = mean of the primary endpoint for the test group, and
  μ_R = mean of the primary endpoint for the reference group

  The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the ratio of the means between test and reference products (μ_T/μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.
- To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error (α) of 0.05, using the mITT population.
- The protocol should include a section with fully detailed statistical analysis plan.
- Study data should be submitted in a standardized format. Applicants should refer to the study data standards published at www.fda.gov[4]
- Applicants should provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:

[4] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm

a. Study identifier
b. Unique subject identifier
c. Subject identifier for the study
d. Study site identifier (if applicable)
e. Age
f. Age units (years)
g. Sex
h. Race
i. Name of planned treatment
j. Name of actual treatment
k. Actual treatment (character)
l. Safety population flag (yes/no)
m. Reason for exclusion from safety population
n. Modified Intent-to-Treat (mITT) population flag (yes/no)
o. Reason for exclusion from mITT population
p. Per-Protocol (PP) population flag (yes/no)
q. Reason for exclusion from PP population
r. Randomized population flag (yes/no)
s. Date/time of first exposure to treatment
t. Date/time of last exposure to treatment
u. End of study date
v. End of study status
w. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
x. Location of Treatment Area
y. Duration of Treatment (total number of TDS applications)
z. VAS (in mm) on Day 0 (baseline)
aa. VAS (in mm) on Day 3 (72 hours after first TDS application)
bb. Any TDS removed due to strong skin irritation reaction (yes/no)
cc. Total number of TDS removed due to strong skin irritation reaction
dd. Any TDS reinforced with tape (yes/no)
ee. Total number of TDS reinforced with tape
ff. Compliance rate (%)
gg. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
hh. Adverse event reported (yes/no)
ii. Concomitant medication (yes/no)

- Applicants should provide basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:

  a. Study identifier
  b. Unique subject identifier
  c. Subject identifier for the study
  d. Study site identifier (if applicable)
  e. Name of planned treatment

f. Name of actual treatment
g. Safety population flag (yes/no)
h. Modified ITT population flag (yes/no)
i. Per-Protocol (PP) 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) (if applicable)
n. Evaluator: identity of evaluator
o. VAS (in mm) at that visit
p. Adhesion score at that visit
q. Concomitant medication reported during this visit (yes/no)
r. Additional treatment required during the visit (yes/no)
s. Adverse event reported during this visit (yes/no)
t. Laboratory testing during this visit (yes/no)

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

- Exclusion Criteria (the sponsor may add additional criteria):
  a. Known allergy or hypersensitivity to diclofenac, aspirin, NSAIDs, adhesives or any excipient in the test product or RLD product.
  b. Known allergy or hypersensitivities to medical adhesives or any component of the test product or RLD.
  c. Medical history of asthma, urticaria, angioedema, bronchospasm, allergic-type reactions after taking aspirin or other NSAIDs, ulcer disease, gastrointestinal bleeding, coagulation defects, hypertension, edema, heart failure or cardiovascular disease.
- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
  a. Nonsteroidal anti-inflammatory drugs (NSAIDs)
  b. Anticoagulants, lithium, digoxin, antidiabetic agents, quinolone antimicrobials, diuretics, ACE inhibitors, immunomodulators or immunosuppressive therapies, interferon, oral, systemic or topical corticosteroids, or cytotoxic drugs.