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Draft – Not for Implementation

Draft Guidance on Diclofenac Epolamine

August 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Diclofenac epolamine

Dosage Form: System

Route: Topical

Strength: 1.3%

Recommended Studies: One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, one in vivo skin irritation and sensitization study, and one comparative clinical endpoint bioequivalence study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1.3%
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
   a. 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*.
   b. Unless otherwise justified, the diclofenac epolamine TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference standard (RS), and worn for 12 hours. Applicants should randomize subjects to receive either the test product or RS 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 pharmacokinetic bioequivalence study.

c. Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics 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 pharmacokinetic bioequivalence study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. 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.
d. The applicant should refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*[a] for the design and conduct of the bioequivalence study with pharmacokinetic endpoints.

Analyte to measure: 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 abbreviated new drug application (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 reference listed drug (RLD)/RS.

2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1.3%
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
    a. The applicant may elect to evaluate the pharmacokinetic bioequivalence (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 bioequivalence, and independently, the comparative assessment of adhesion.
    b. The applicant should refer to the most recent version of the FDA guidance for industry on *Assessing Adhesion With Transdermal and Topical Delivery Systems*

for ANDAs[a] for the design and conduct of the independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat design in vivo
Strength: 1.3% (administered as one-fourth of the test product and one-fourth of the RS)
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:
   a. All test articles (i.e., one-fourth of the test product[1], one-fourth of the RS, optional vehicle TDS[2], and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended in the approved labeling for the RS.
   b. Sequential TDS applications should be made to the same application site every 24 hours for a total of 21 consecutive days.
   c. There is insufficient information to determine whether it is safe to simultaneously apply two whole, diclofenac epolamine TDS on the same subject during a 21-day skin irritation and sensitization study. Since the RLD/RS has a matrix design that can be safely cut, the test product is anticipated to have a design that can also be safely cut to a smaller size. One-fourth of the test product may be applied simultaneously with one-fourth of a RS (to separate skin sites) for conducting this study. It would not be acceptable to manufacture a separate batch of the test TDS in order to use a smaller TDS in this study.
   d. The applicant should refer to the most recent version of the FDA guidance on *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*[a] for the design and conduct of the skin irritation and sensitization study.

4. Type of study: Comparative clinical endpoint bioequivalence study
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.
   a. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of acute ankle pain due to a minor ankle sprain. Subjects should be randomized to receive the test product, RS, 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).
   b. Inclusion criteria (the applicant may add additional criteria):

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

- 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 baseline self-evaluation of acute ankle pain on active mobilization by the VAS ≥ 50 mm

c. Exclusion criteria (the applicant may add additional criteria):
    - Pregnant or lactating female
    - Sprain occurred > 48 hours prior to study enrollment
    - Ankle sprain requires an orthopedic or surgical treatment
    - Ankle sprain treated prior to study entry by topical, oral, or parenteral non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy, ultrasound, physical therapy or acupuncture
    - Non-intact or damaged skin within the area to be treated, e.g., eczema, psoriasis, exudative dermatitis, infected lesion, burn or wound
    - Medical history of asthma, urticaria, angioedema, bronchospasm, ulcer disease, gastrointestinal bleeding, coagulation defects, hypertension, edema, heart failure or cardiovascular disease
    - Medical history of any chronic pain disorder
    - Severe cardiac, renal or hepatic impairment
    - Severe systemic disease (e.g., cancer, severe acute infection)
    - Use within one month prior to randomization of (1) immunomodulators or immunosuppressive therapies, (2) interferon, (3) oral or parenteral corticosteroids or (4) cytotoxic drugs
    - Use within 7 days prior to randomization of any topical agent on the affected ankle
    - Use within 7 days prior to randomization of topical, oral or parenteral treatment with NSAIDs or aspirin
    - Use within 12 hours prior to randomization of an analgesic
    - Known allergy or hypersensitivity to diclofenac, aspirin or other NSAIDs, or any excipient in the test product or RS

d. 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:
    - Any therapy for treatment of pain, e.g., oral, topical, or parenteral NSAIDs, aspirin or narcotic pain medication, other than study treatment.
    - Anticoagulants, lithium, digoxin, antidiabetic agents, quinolone antimicrobials, diuretics, angiotensin-converting-enzyme (ACE) inhibitors, immunomodulators or immunosuppressive therapies, interferon, oral, systemic or topical corticosteroids, or cytotoxic drugs.
    - Topical product other than the assigned treatment (including moisturizers, sunscreen, creams, ointments, lotions, and powders) applied on or near the treatment area.
    - Treatment to the affected ankle, e.g., physiotherapy, ultrasound, physical therapy or acupuncture.

- 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.

e. 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 VAS in mm.

f. 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 RS with regard to the expected and unexpected application site reactions.

g. Adhesion should be monitored during the course of the study to document the adequacy of skin contact. Applicants may consider establishing criteria for using tape to reinforce any TDS that are lifting during the study.

h. The applicant should refer to the most recent version of the FDA guidance for industry on *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*[a] regarding the scoring system used to monitor TDS adhesion during the study.

i. Applicants should provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    - Study identifier
    - Unique subject identifier
    - Subject identifier for the study
    - Study site identifier (if applicable)
    - Age
    - Age units (years)
    - Sex
    - Race
    - Name of planned treatment
    - Name of actual treatment
    - Actual treatment (character)
    - Safety population flag (yes/no)
    - Reason for exclusion from safety population
    - Modified Intent-to-Treat (mITT) population flag (yes/no)
    - Reason for exclusion from mITT population
    - Per-Protocol (PP) population flag (yes/no)
    - Reason for exclusion from PP population
    - Randomized population flag (yes/no)

- Date/time of first exposure to treatment
- Date/time of last exposure to treatment
- End of study date
- End of study status
- Subject required additional treatment due to unsatisfactory treatment response (yes/no)
- Location of Treatment Area
- Duration of Treatment (total number of TDS applications)
- VAS (in mm) on Day 0 (baseline)
- VAS (in mm) on Day 3 (72 hours after first TDS application)
- Any TDS removed due to strong skin irritation reaction (yes/no)
- Total number of TDS removed due to strong skin irritation reaction
- Any TDS reinforced with tape (yes/no)
- Total number of TDS reinforced with tape
- Compliance rate (%)
- Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
- Adverse event reported (yes/no)
- Concomitant medication (yes/no)

j. Applicants should provide basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
   - Study identifier
   - Unique subject identifier
   - Subject identifier for the study
   - Study site identifier (if applicable)
   - Name of planned treatment
   - Name of actual treatment
   - Safety population flag (yes/no)
   - Modified ITT population flag (yes/no)
   - Per-Protocol (PP) population flag (yes/no)
   - Analysis date
   - Analysis visit
   - Study visit within the designated window (yes/no)
   - Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
   - Evaluator: identity of evaluator
   - VAS (in mm) at that visit
   - Adhesion score at that visit
   - Concomitant medication reported during this visit (yes/no)
   - Additional treatment required during the visit (yes/no)
   - Adverse event reported during this visit (yes/no)
   - Laboratory testing during this visit (yes/no)

k. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for comparative clinical endpoint bioequivalence study.

l. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

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.

1. 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 RS
    b. Known allergy or hypersensitivities to medical adhesives or any component of the test product or RS
    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

2. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
    a. 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

Additional information:

Device:
The RLD is a TDS and a drug-device combination product.

FDA recommends that prospective applicants examine the size and shape and external critical design attributes of the RLD device when designing the test device.

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA

guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.