Development of Locally Applied Corticosteroid Products for the Short-Term Treatment of Symptoms Associated with Internal or External Hemorrhoids

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Benjamin Vali at 301-796-4261.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

Development of Locally Applied Corticosteroid Products for the Short-Term Treatment of Symptoms Associated with Internal or External Hemorrhoids

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

TABLE OF CONTENTS

Development of Locally Applied Corticosteroid Products for the Short-Term Treatment of Symptoms Associated with Internal or External Hemorrhoids[1]
Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of locally applied corticosteroid products (including suppositories or products that require an applicator) for the short-term treatment of symptoms associated with internal or external hemorrhoids. Specifically, this guidance describes FDA's current thinking regarding the recommended attributes of patients for enrollment, efficacy assessments, and safety assessments.[2]

This guidance does not address the clinical development of drugs for the chronic treatment of signs and symptoms associated with internal or external hemorrhoids or drugs for the treatment of an underlying disease.

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.

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Error Products (Division) in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the Division to discuss specific issues that arise during the development of products.

II. BACKGROUND

Hemorrhoids represent one of the most common medical and surgical disease conditions in the United States, accounting for over 2.5 million outpatient evaluations per year.[3] Hemorrhoids are dilated arteriovenous connective tissues that are normally present between the anal mucosa and underlying internal sphincter and are usually categorized as internal or external hemorrhoids based upon their location with respect to the dentate line.

Because the pathogenesis of hemorrhoids involves anatomic structural changes in the vascular cushions (hemorrhoidal arteriovenous plexus), surrounding supportive muscles, connective tissues, and skin, rectal bleeding commonly associated with internal hemorrhoids is unlikely to be improved with locally applied corticosteroid products. However, many patients have one or more additional perirectal symptoms (e.g., itch, discomfort, pain, or burning) because of secretions from inflamed hemorrhoids that irritate the skin. These perirectal symptoms are common in patients with both external and internal hemorrhoids and may be mitigated by locally applied corticosteroid products.

Fit-for-purpose[4] patient-reported outcome (PRO) instruments[5] for evaluating symptomatic treatment response in internal or external hemorrhoids should be identified and agreed upon with FDA for regulatory use.

III. TRIAL POPULATION

Sponsors developing locally applied corticosteroid products for the short-term treatment of symptoms associated with internal or external hemorrhoids should consider the following for clinical trial populations:

- To be enrolled, patients should be sufficiently symptomatic, with a minimum level of symptomatology (e.g., severity or frequency) to allow observation of a clinically meaningful improvement. We recommend that sponsors include a screening period

[3] Peery AF, SD Crockett, CC Murphy, JL Lund, ES Dellon, JL Williams, ET Jensen, NJ Shaheen, AS Barritt, SR Lieber, B Kochar, EL Barnes, YC Fan, V Pate, J Galanko, TH Baron, and RS Sandler, 2019, Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018, Gastroenterology, 156(1):254–272.

[4] A conclusion that the level of validation associated with a tool is enough to support its context of use. See the glossary of the Biomarkers, EndpointS and other Tools (BEST) Resource: https://www.ncbi.nlm.nih.gov/books/NBK338448/.

[5] A PRO is a type of clinical outcome assessment that is a measurement based on a report that comes directly from a patient (i.e., trial subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient can be measured only by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. See the glossary of the BEST Resource.

before randomization to document persistence of symptoms and train patients to collect PRO data appropriately.

- As symptoms are more likely to be present in patients with grade 3 or grade 4 internal hemorrhoids and external hemorrhoids, we recommend that sponsors enroll adequate numbers of such patients.

- Sponsors should diagnose and classify internal hemorrhoids by proctoscopy or anoscopy and document internal hemorrhoids by photograph or video recording as per clinical practice guidelines of the American Society of Colon and Rectal Surgeons.[6]

- Patients with perirectal conditions, such as perianal warts, anorectal fistula, and anal fissure, which may present with perirectal symptoms similar to those accompanying hemorrhoids (e.g., itch, discomfort, pain, or burning), should be excluded.

- Because narcotics use is known to cause constipation and exacerbate symptoms associated with hemorrhoids and could influence efficacy assessment, sponsors should exclude patients using narcotics.

- Because intake of extra fiber and water could improve constipation and symptoms associated with hemorrhoids, patients should not make dietary changes before-enrollment and throughout the duration of the trial.

IV. DEVELOPMENT PROGRAM

A. Trial Design

Sponsors developing locally applied corticosteroid products for the short-term treatment of symptoms associated with internal or external hemorrhoids should consider the following for clinical trial design:

- We recommend a multicenter, randomized, double-blind, vehicle-controlled, parallel group trial design with a prespecified screening period before randomization of patients to confirm eligibility criteria.

- The trial duration and timing of efficacy assessments should be guided by the mechanism of action of the drug and its expected onset of action and the time frame in which a clinical benefit is expected to be observed. We recommend a treatment period of at least 2 weeks' duration to assess efficacy.

[6] Davis BR, SA Lee-Kong, J Migaly, DL Feingold, and SR Steele, 2018, The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Hemorrhoids, Dis Colon Rectum, 61(3):284–292.

- Following the randomized treatment phase, there should be a 2- to 3-week follow-up period off treatment (see section IV. D., Safety Considerations) to assess safety, durability of response, and the potential need for retreatment.

- Where uncertainty exists regarding time to onset of clinical benefit, optimal dosage, and optimal duration of therapy, we strongly encourage a phase 2 trial to address these issues before embarking on a large phase 3 program.

B Efficacy Considerations

Sponsors developing locally applied corticosteroid products for the short-term treatment of symptoms associated with internal or external hemorrhoids should consider the following regarding a drug's efficacy:

- For the primary endpoints in phase 3 trials, sponsors should identify a response that represents meaningful improvement from baseline in symptoms, compared with vehicle control, using a well-defined and reliable PRO instrument's endpoint scores.

- Statistically significant but small group-level mean differences may not establish whether the effect is clinically meaningful.

  – To aid in interpreting the PRO endpoint results, sponsors should propose a range of thresholds that would constitute a clinically meaningful within-patient score change using anchor-based methods (e.g., patient global impression of symptom severity scale as an anchor) in conjunction with empirical cumulative distribution functions (eCDFs) of individual patient changes in scores using data pooled across trial arms with separate curves for each anchor response category.

    - Additionally, sponsors should submit for review a supportive graph (i.e., eCDF) of within-patient changes in scores from baseline with separate curves for each treatment arm. The graph will be used to assess whether the treatment effect occurs in the range that patients consider to be clinically meaningful.

C. PRO Endpoints

Sponsors developing locally applied corticosteroid products for the short-term treatment of symptoms associated with internal or external hemorrhoids should consider the following when selecting a fit-for-purpose PRO instrument:

- FDA encourages sponsors to seek FDA input as early as possible and at important milestones throughout the drug development process to ensure that fit-for-purpose PRO instruments are included in phase 3 trials. For general recommendations regarding PRO instruments and the documents to be provided to FDA for review, see the guidance for industry relevant to patient-reported outcome measures or clinical outcome assessments.

- FDA recommends selecting a PRO instrument based on patient input regarding the most important and bothersome perirectal symptoms of internal or external hemorrhoids (e.g., itch, discomfort, pain, or burning) and choosing for assessment symptoms that are expected to improve with the treatment. FDA encourages sponsors to first explore using existing PRO instruments for assessing patients' symptoms before developing a de novo PRO instrument.

  - Examples of patient-reported symptom severity assessment scales that may be fit-for-purpose include an 11-point (i.e., 0 to 10) numeric rating scale or a verbal rating scale (e.g., none, mild, moderate, severe) that asks patients daily to rate their worst experience of one or several specific perirectal symptoms (e.g., itch, discomfort, pain, or burning) over the past 24 hours. Additionally, a frequency scale for one or more of these items may also be considered (e.g., ranging from "none of the time" to "all of the time").

  - To minimize patient recall error and measurement error, sponsors should use instruments that are administered daily (e.g., 24-hour recall period) and that focus on capturing patients' symptoms. Patients should complete the PRO instruments at the same time each day (e.g., evening before bedtime). Improvement in, or resolution of, symptoms should be demonstrated for a meaningful, prespecified duration of time (e.g., one week), not based solely on a single day's assessment.

    - For newly developed instruments, or existing instruments that have not been tested in the target patient population, it may be useful for sponsors to test the appropriateness and clarity of any proposed PRO instruments' instructions, recall period, items, and response options by conducting cognitive interviews with a number of patients (e.g., 8 to 10 patients) matching the target population to decrease the possibility of introducing measurement error because of patients' misunderstanding or incomplete understanding of the PRO instruments.

    - When modifying an existing instrument or developing a new PRO, sponsors should consider that phase 2 trials should help inform finalization of scoring algorithms and endpoint definitions. Piloting the proposed PRO instrument in phase 2 trials can provide sponsors an opportunity to evaluate the instrument's psychometric properties and performance (reliability, validity, and ability to detect change) as well as provide guidelines for interpreting clinically meaningful within-patient change in scores and confirm the endpoint definition. Pilot results can further inform plans for implementing the proposed instruments in phase 3 trials.

    - We recommend that sponsors analyze PRO endpoints as continuous or ordinal variables, with the choice justified based on the nature of the data, using baseline values as covariates. FDA does not recommend a responder analysis endpoint or a percentage change from baseline endpoint unless the targeted response is complete resolution of symptoms. The statistical analysis plan should include

prespecified alternative approaches for analysis if extreme outliers occur, such as analyses based on ranks.

D. Safety Considerations

Sponsors developing locally applied corticosteroid products for the short-term treatment of symptoms associated with internal or external hemorrhoids should consider the following regarding safety in clinical trials:

- For products being studied over a 2-week course of treatment, we recommend at least one interim assessment to capture potential adverse events (which can be completed by telephone) and a minimum follow-up period of 2 to 3 weeks after treatment is discontinued to adequately assess safety (duration, severity, progression or resolution of any reported adverse events).

- Safety assessment at the end of the trial or at drop-out should include assessing changes in the perirectal skin, such as thinning or atrophy of skin.

- We recommend that hypothalamic pituitary adrenal (HPA) axis suppression potential be studied by an adrenocorticotropic hormone (ACTH) stimulation test. The ACTH stimulation test should be performed at preestablished time points with at least a 4-week interval between the pre- and posttreatment assessments. For trials lasting less than 4 weeks, the ACTH stimulation test for determining baseline status should be completed early in the screening period to permit an adequate amount of time between the pre- and posttreatment assessments. The ACTH stimulation test may be performed in a dedicated study or during phase 2 or phase 3 trials. Patients showing signs of HPA axis suppression or having abnormal ACTH stimulation test results at the end of treatment should be followed closely until complete resolution.

  Sponsors intending to rely on another approved corticosteroid product to support absence of HPA axis suppression from the systemic absorption of the proposed product should demonstrate that the relative bioavailability of the proposed product is no greater than that of the approved corticosteroid product that has been shown to cause no HPA axis suppression.

E. Additional Considerations

If the proposed drug product will be copackaged with a device (e.g., an applicator), it would probably be considered a drug-device combination product as defined in 21 CFR 3.2(e). Sponsors should meet with the Division about combination product status considerations early in the development process; sponsors are encouraged to consult the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).[7]

[7] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.