Guidance for Industry

Migraine: Developing Drugs for Acute Treatment

DRAFT GUIDANCE

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

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the acute treatment of migraine.[2] Specifically, this guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs to support drugs for the acute treatment of migraine. This draft guidance is intended to serve as a focus for continued discussions among the Division of Neurology Products, pharmaceutical sponsors, the academic community, and the public.[3] This guidance does not address the development of drugs indicated to reduce the frequency of migraine attacks. That issue will be addressed separately in a future guidance.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

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

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the acute treatment of migraine.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

FDA's guidance documents, including this guidance, 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.

II. BACKGROUND

Migraine is a chronic neurovascular disorder characterized by recurrent attacks of often severe headache, typically presenting with nausea and sensitivity to light and/or sound. In adults, migraine attacks usually last from 4 to 72 hours. Migraine headache is typically throbbing, unilateral, and aggravated by physical activity. Criteria proposed by the International Headache Society (IHS) require a combination of some of these characteristics and associated symptoms in at least five attacks to establish a diagnosis of migraine.[5]

There are two major subtypes of migraine: migraine without aura (also called *common migraine*) and migraine with aura (also called *classic migraine*). Migraine with aura is characterized by focal neurological symptoms that typically precede, or sometimes accompany, the headache. These focal neurological symptoms are absent in migraine without aura. Some patients may present with both subtypes of migraine.

Pharmacologic approaches to the treatment of migraine include drugs to treat acute migraine attacks as they arise (acute treatment of migraine), and drugs to reduce the frequency of migraine attacks (preventive treatment). This guidance addresses the development programs of drugs for the acute treatment of migraine.

III. DEVELOPMENT PROGRAM

A. Trial Population

Either healthy adult volunteers or migraine patients can be enrolled in initial phase 1 trials. Because migraine patients are predominantly female, it is important to enroll, early in development, women of child-bearing potential who are practicing effective contraception.

Because migraine peak incidence is during adolescence, and onset in younger children is not uncommon, pediatric studies of children aged 6 years and older are required under the Pediatric Research Equity Act. Sponsors are encouraged to begin discussions about their pediatric clinical development plan early in development because sponsors are required to submit pediatric study

[5] See http://ihs-classification.org/en/.

plans no later than 60 days after an end-of-phase 2 meeting.[6] Sponsors should refer to the Pediatric Research Equity Act as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA).[7]

B. Efficacy Considerations

Sponsors should consider the usual efficacy standards for this indication. Typically, two adequate and well-controlled trials are needed to support approval of a new molecular entity (see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). A single adequate and well-controlled trial may be sufficient to support approval of a new route of administration for a drug already approved for the acute treatment of migraine, or for treatment of a new subpopulation (e.g., for the pediatric population).

1. Trial Design

In general, efficacy trials should use a randomized, double-blind, placebo-controlled, parallel group design. Although a comparison of a single dose level with placebo can be used to support efficacy of a drug, it is usually preferable to study at least two doses. Consideration should also be given to the use of an active control (i.e., a drug approved for the acute treatment of migraine), in addition to a placebo control, to assess the assay sensitivity of the trial. Use of an active control for assay sensitivity cannot provide substantial evidence for comparative claims in labeling and promotion unless the trial is designed to support that objective.

The timing of drug administration should be defined in the protocol. Although drug administration as early as practicable during the course of acute migraine is typically recommended by migraine experts, evidence should be obtained that the investigational drug is able to treat a migraine headache of moderate or severe intensity, because many patients quickly reach that level of pain. Therefore, in registration trials, migraine patients should take the investigational drug at the earliest time they experience a migraine headache of moderate or severe intensity. It is also important to collect sufficient baseline information about the headache (i.e., headache intensity, presence or absence of associated symptoms, unilaterality or bilaterality of the headache, aggravation by exercise, throbbing or nonthrobbing) to be able to verify that the headache treated was, in fact, acute migraine. Trials assessing drug response after treatment of

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[6] See the Pediatric Research Equity Act (Public Law 108-155; section 505B(e)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355B) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) (Public Law 112-144).

[7] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the FD&C Act; 21 U.S.C. 355B) as amended by FDASIA (Public Law 112-144) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ155.108). The Pediatric Research Equity Act was amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA), Title IV, Pediatric Research Equity Act of 2007 (http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm) and FDASIA (http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf).

acute migraine at the mild pain stage can be conducted in addition to the pivotal efficacy trials, and can be described in labeling.

Typically, efficacy trials should assess the effectiveness of a single dose of the investigational drug to treat a single acute migraine episode. To assess the safety and efficacy of redosing (e.g., in case of migraine symptom(s) recurrence or incomplete response), patients should be re-randomized to investigational drug or control. The interval before redosing should be chosen carefully, with consideration of the pharmacokinetics of the drug.

2. Trial Population and Entry Criteria

Patients enrolled in clinical trials should have a diagnosis of migraine, with or without aura, according to established IHS criteria. The age at the time of initial migraine diagnosis should be younger than 50 years old to decrease the chance of enrolling patients with other diagnoses. The time since original diagnosis should be at least 1 year. Patients with coexisting types of headaches (e.g., tension-type headaches) can be included in the trial if the other headaches are distinguishable from migraine headache by the patient. Concomitant treatment used to reduce the frequency of migraine episodes can be allowed, but only if the treatment has been stable for at least 3 months before inclusion into the trial. If the trial population includes patients with and without concomitant treatment to reduce the frequency of migraine episodes, randomization should be stratified by use/non-use of such concomitant treatment.

3. Dose Selection

The first controlled trials should explore a range of doses to describe the dose-response relationship and provide a basis for dose selection in definitive efficacy trials. Some data should be collected on doses above and below what appears to be the optimal dose, and an effort should be made to identify the lowest dose that provides a desirable treatment effect. It is advisable, whenever feasible, to obtain drug plasma level data on patients. Establishing a plasma concentration (exposure)-response relationship can be useful to support dosing recommendations based on specific patient characteristics (e.g., body weight, renal function).

4. Concomitant Medications

During the conduct of early trials, and until the drug's metabolism is adequately understood, concomitant medications should be avoided. Assuming there are no important drug interactions anticipated, concomitant medications to reduce the frequency of migraine episodes can be used in later stage trials. If drugs used for the preventive treatment of migraine are withdrawn, withdrawal should be complete at least 1 month before trial entry.

It is important that patients avoid any analgesic or other acute migraine medication(s) for at least 24 hours before treatment with the investigational drug to reduce confounding factors. Use of rescue medication must be allowed, but patients should be encouraged to wait at least 2 hours after initial treatment before using rescue medication. Rescue medication can consist of the patient's usual acute treatment of migraine, unless this treatment has the potential for an adverse

interaction with the investigational drug (e.g., 5-HT_1 agonist or ergot alkaloid medications should be avoided within 24 hours of any investigational 5-HT_1 agonist or vasoactive drug use).

5. Efficacy Endpoints

Because migraine is a complex disorder characterized by, in addition to headache, several associated symptoms (i.e., nausea, photophobia, and phonophobia), a drug effect on headache pain alone is not considered sufficient to grant a claim for the acute treatment of migraine. In the past 2 decades, approval of drugs for the acute treatment of migraine involved the demonstration of an effect on 4 co-primary endpoints: pain, nausea, photophobia, and phonophobia. More recently, approval based on an effect on headache pain and nausea as co-primary endpoints has been considered. An alternative approach would consist of having patients prospectively identify their most bothersome migraine-associated symptom in addition to pain. Using this approach, the two co-primary endpoints would be (1) having no headache pain at 2 hours after dosing and (2) a demonstrated effect on the most bothersome migraine-associated symptom at 2 hours after dose. Regardless of the associated symptom identified as most bothersome, all three important migraine-associated symptoms (i.e., nausea, photophobia, and phonophobia) should be assessed as secondary endpoints.

In general, migraine-associated headache pain and associated symptoms should be measured by asking patients to self-report the current status of their headache pain and associated symptoms. A four-point Likert scale should be used for headache pain (i.e., 0=none, 1=mild, 2=moderate, 3=severe), while a binary scale (present or absent) should be used for associated symptoms.

The following additional secondary endpoints should be assessed in efficacy trials:

- The probability of achieving "no headache pain" at various time points following treatment. For this analysis, it is especially useful to record the time that no headache pain is first noted.

- The probability of requiring additional medication (either a second dose or rescue medication) within 24 hours of initial treatment.

- The proportion of patients who are "sustained pain-free," defined as having no headache pain at 2 hours after dose, with no use of rescue medication and no relapse of headache pain within 24 hours (24-hour sustained pain-free) or 48 hours (48-hour sustained pain-free) after administration of the investigational drug. The proportion of patients who are sustained pain-free should not be used as a primary endpoint, because it is possible to show a significant effect on the proportion of patients who are sustained pain-free without any significant drug effect on individual migraine symptoms (including pain) by the 2-hour time point.

- The incidence of pain relapse, defined as the return of headache of any severity within 48 hours after administration of the investigational drug, when the patient was pain-free at 2 hours after investigational drug administration.

6. Trial Procedures and Timing of Assessments

The treatment observation period should be at least 48 hours and include data collection at prespecified time points during the observation period (e.g., 0, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hours). For outpatient trials, the patient should be instructed to record all data in a headache diary. The headache diary should be shown to be well defined and reliable for the target population based on the recommendations described in guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

7. Statistical Considerations

The typical primary efficacy analysis should compare the proportion of patients in each treatment group with no headache pain (headache pain score = 0) at 2 hours after investigational drug administration, and the proportion of patients in each treatment group with absence of the "most bothersome associated symptom" at 2 hours after investigational drug administration. No correction for multiple comparisons is necessary for these two co-primary endpoints, because both must show a statistically significant effect of treatment.

Sponsors should perform an analysis that compares the proportion of patients who achieve headache *response* (defined as a grade 2 or 3 headache at baseline that, when treated, becomes a grade 0 or 1 headache at a prespecified time point).

The choice of secondary endpoints should be based on the trial objectives and intended claims in labeling. Typically, secondary endpoints should not reflect an effect on the primary endpoint, and should measure different domains or drug effects. It is important to predefine the secondary endpoints, and include a statistical plan to deal with multiple comparisons.

C. Safety Considerations

Treatment of acute migraine headaches is considered to be chronic-intermittent treatment. Therefore, the safety database should follow the same general paradigm as for chronic-use drugs, including the conduct of at least one long-term safety trial during which patients can treat all acute migraine episodes with the investigational drug.

Because phase 3 trials are typically conducted in the outpatient setting, phase 1 and early phase 2 trials, during which the investigational drug is administered under close medical supervision, provide the best opportunity to obtain vital sign and laboratory data at times close to investigational drug administration. These trials should include vital signs, hematology, serum chemistry, urinalysis, and 12-lead electrocardiogram at appropriate intervals. Vital signs and electrocardiography should be assessed around expected C_{max} for the investigational drug and major metabolites. During most short-term phase 2 and phase 3 outpatient trials, baseline and post-treatment vital signs and laboratory assessment should be conducted. Safety data during long-term phase 3 trials should be obtained at appropriate intervals, taking into consideration nonclinical and earlier human experience with the investigational drug and with other drugs of the class.

For new molecular entities, the safety recommendations in the ICH guidance for industry *E1 The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* apply. To be counted in the long-term safety database, adult patients should treat, on average, a minimum of two migraine attacks per month. We anticipate a database of chronic intermittent use in at least 300 patients using the drug for 6 months, and 100 patients using the drug for 1 year. The safety experience should be at relevant doses and frequency of administration, including a substantial experience at the highest dose and highest frequency of administration proposed for marketing.

If the drug is suspected or known to have vascular activity, additional safety trials in vulnerable populations (e.g., patients with known coronary artery disease) may be needed. Consultation with the review division is advised.

Sponsors should assess the occurrence of medication overuse headache, which occurs when patients escalate the frequency of use of acute migraine drugs.

D. Other Considerations

1. Pediatric Studies

Migraine is a relatively common disorder in children. There are reasons to believe that migraine in the adult and pediatric populations are substantially different clinical entities and one cannot assume that a drug effective in adults will also be effective in children. Therefore, studies in the pediatric population are needed. Because migraine is rare in children younger than 6 years old, a partial waiver to the conduct of studies for this age group generally will be granted. Sponsors are encouraged to begin discussions about their pediatric clinical development plan early in development because they are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting.[8] Pediatric studies should evaluate patients aged 6 to 17 years. Because disease characteristics change with puberty, pediatric studies should include a sufficient number of patients aged 6 to 11 years and 12 to 17 years to characterize adequately the safety and efficacy of the drug in these 2 age groups. Migraine diagnosis should be based on IHS criteria. We recommend that sponsors refer to the Pediatric Research Equity Act as amended by FDASIA[9] to review requirements for submission of an initial pediatric study plan.[10]

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[8] See the Pediatric Research Equity Act (Public Law 108-155; section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355B) as amended by FDASIA (Public Law 112-144).

[9] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the FD&C Act; 21 U.S.C. 355B) as amended by FDASIA (Public Law 112-144) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_public_laws&docid=f:publ155.108). The Pediatric Research Equity Act was amended by FDAAA, Title IV, Pediatric Research Equity Act of 2007 (http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm) and FDASIA (http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf).

[10] See the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

Before initiation of a clinical efficacy trial, the pharmacokinetics of the drug in the pediatric population should be assessed and compared with the pharmacokinetics of the drug in adults. This permits proper dose selection for pediatric efficacy and safety studies. The development of age-appropriate formulation for pediatrics also should be considered as needed.

Sponsors can consider the following two options for their pediatric efficacy studies programs:

(1) Conduct separate efficacy studies, one in patients aged 12 to 17 years and a second in patients aged 6 to 11 years

(2) Conduct a single efficacy study in patients aged 6 to 17 years, with a sufficient number of patients in the 6 to 11-year and 12 to 17-year subgroups to be able to characterize the efficacy (and safety) of the drug in each subgroup adequately

Because of the high placebo response rate in migraine pediatric studies, an enrichment strategy should be considered to increase the chance of demonstrating a drug effect. An approach that has proven successful in several pediatric trials is, during a migraine attack, to first administer single-blind placebo in all patients, and then randomize patients to the investigational drug or placebo only those patients who did not achieve pain freedom at 30 minutes after single-blind placebo. Also, only patients who typically experience migraine attacks lasting at least 3 hours should be included. The proportion of patients pain-free at 2 hours after administration of the investigational drug should be the primary endpoint. An approach that evaluates pain and another symptom (i.e., co-primary endpoints) is not needed for pediatric studies. Migraine-associated symptoms should be evaluated as secondary endpoints. It is not necessary to evaluate other endpoints as co-primary endpoints in the pediatric studies. Other secondary endpoints as described above for adult trials also should be evaluated.

A 1-year long-term pediatric safety study should be conducted. Generally, if the drug is already approved in adults, the pediatric safety database should include data on at least 200 patients treating, on average, one migraine attack per month for 6 months; and 75 patients treating, on average, at least one migraine attack per month for 1 year. That study should evaluate the effect of treatment on growth, cognition, and endocrine development.

2. Labeling Considerations

Over the past 2 decades, the FDA has approved several new drugs indicated for the treatment of acute migraine for marketing in the United States. The majority of these are selective 5-$HT_{1B/1D}$ receptor agonists and thus belong to the drug class referred to as *triptans*. The principal safety concern with triptans relates to their ability to cause coronary or peripheral arterial constriction that may result in serious adverse cardiac or peripheral vascular events. As a result, the FDA has adopted certain standard or *class labeling* for triptans. Future investigational drugs with similar pharmacological activity are subject to this class labeling, unless it can be shown that the drug does not have vasoconstrictive effects. Also, new drugs of other pharmacological classes that also have the potential for vasoconstrictive effects probably would be subject to similar class labeling.

The latest approved labeling for a member of this class should form the basis, or *template*, for labeling of new drugs that share a similar mechanism of action, or have potential vasoconstrictive effects. As is always the case, any additional information regarding the safe use of a drug should be included in the appropriate sections of labeling, even though it may not be described in this guidance.

The recommendations for the following labeling sections apply to all new drugs indicated for the acute treatment of migraine.

- **INDICATIONS AND USAGE**

  This section should be brief and should state that the drug is indicated for the acute treatment of migraine with or without aura.

- **DOSAGE AND ADMINISTRATION**

  This section should include the following information:

  – The minimum interval between doses to treat the same acute migraine episode (i.e., if the migraine episode has not resolved by 2 hours after taking the drug, or returns after a transient improvement). Re-dosing information should be described in labeling only if information supporting the safety and efficacy of re-dosing is included in the new drug application.

  – The average number of acute migraine episodes within a 30-day period that can be treated safely (based on data obtained from the long-term safety trials).

- **WARNINGS AND PRECAUTIONS**

  This section should include a description of medication overuse headache as follows:

  Medication Overuse Headache
  Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (i.e., medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

- **CLINICAL STUDIES**

  This section should describe the efficacy trials from which evidence of effectiveness was obtained. The results of the primary efficacy analyses should be displayed in a single table, showing the results of each trial separately, and showing dose-response

information. In general, active comparator data should not be presented unless they represent substantial evidence based on clinical trials designed to adequately and fairly assess the comparative effectiveness of the drugs.

This section also should include a figure derived using a Kaplan-Meier survival analysis method showing the estimated probability of achieving an initial headache response within the first 2 hours following the initial dose. Pooled efficacy data from similarly designed controlled trials can be used to generate these graphs. If there are dose-response data, these should be shown. A brief statement describing the dose-response relationship of the drug, as well as brief statements regarding efficacy in important subgroups (e.g., sex, age, and race) also should be included.