European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 January 2007
Doc. Ref. CPMP/EWP/788/01 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF MIGRAINE

DRAFT REVISION* AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	26 January 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2006
AGREED BY THE EFFICACY WORKING PARTY	9 January 2007
ADOPTION BY CHMP	24 January 2007
DATE FOR COMING INTO EFFECT	31 July 2007

This guideline replaces guideline: CPMP/EWP/788/01

*IMPORTANT: The revision relates to the paediatric section only. Therefore, it is only the paediatric section (3.3.1) of this guideline and the attached Annex, which have been updated

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF MIGRAINE

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Guideline is intended to provide guidance on the clinical development of new medicinal products in the treatment of migraine. This Guideline should be read in conjunction with Directive 2001/83/EC, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),
- Dose-Response Information to Support Drug Registration (ICH E4),
- General Considerations for Clinical Trials (ICH E8),
- Statistical Principles for Clinical Trials (ICH E9),
- Choice of Control Group in Clinical Trials (ICH E10),
- Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11),
- Pharmacokinetic Studies in Man (Eudra/C/ 87/013),
- Investigations of Drug Interactions (CPMP/EWP/560/95),
- Applications with 1.) Meta-analyses and 2.) One Pivotal Study (CPMP/2330/99),
- Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)

This Note is intended to assist applicants during the development of medicinal products for the treatment of migraine. It is only guidance; any deviation from guidelines should be explained and discussed in the Expert reports/ Clinical Overview.

INTRODUCTION (BACKGROUND)

Migraine is a disease with recurrent headache attacks usually accompanied by nausea, vomiting, photo- and/or phonophobia. In adults, an attack may last for 4-72 hours. Two main types of migraine are distinguished, migraine with aura and without aura. In migraine with aura the headache is preceded by reversible neurological symptoms.

Investigations of regional cerebral blood flow demonstrate a slowly spreading hypoperfusion during the aura. It is possible that this spreading hypoperfusion is caused by a neurophysiological phenomenon akin to cortical spreading depression of Leao [1]. In migraine without aura the regional cerebral blood flow remains normal. The pathophysiological mechanisms of the migraine pain remain elusive but the pain is most likely due to some activation of the trigeminovascular system.

The one-year prevalence in adults is estimated to be 15%. In children and adolescents the prevalence is approximately 5 %. Three times as many women are affected as men and most sufferers are aged between 20 and 50 years; prevalence declines after 50 years. Lost workdays per year due to migraine in the general employed population have been estimated at almost 6 days per 1000 working persons. Migraine is treated with agent(s) for the acute attack, with prophylactic agents, or both. A patient who is not satisfactorily managed with acute treatment may receive prophylactic treatment, which is usually started at an attack rate of 2 or more per month.

Current acute treatments are either unspecific or specific for migraine. Unspecific (symptomatic) agents include NSAIDs and common analgesics with or without antiemetics. Migraine specific agents include ergot alkaloids and triptans. The specific antimigraine agents are thought to exert their effect by selective constriction of cranial arteries and inhibition of the trigeminovascular system.

The agents usually used for migraine prophylaxis include certain beta-blockers, some calcium-blockers, some antiepileptics, antiserotonin agents including methysergide and the tricyclic antidepressants. For the majority of these drugs, the mode of action is still unknown.

Naturally, trials for acute treatment and prophylaxis of migraine have different designs. In addition, short-term prophylaxis is sometimes used to prevent predictable migraine attacks, such as those associated with the menstrual cycle (see Section 3.3.3).

The subsequent parts of this note will distinguish, when appropriate, clinical development of medicinal product for treatment of acute migraine attack and for migraine prophylaxis.

A clinical development programme for anti-migraine agents should follow state-of-the-art within current scientific and clinical practice. Topics addressed in this Note for Guidance are intended to comply with International Headache Society Headache Classification Subcommittee [2].

1. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

The diagnostic criteria should conform to state-of-the-art, e.g. those of the International Headache Society (IHS), presently International Headache Society Classification Subcommittee, International classification of headache disorders [2]. Inclusion of patients not adhering to these criteria should be justified. Patients having in addition other type(s) of headaches need not be excluded if they can differentiate them from migraine by the quality of pain (one sided, pulsating, aggravated by activity and/or moderate or severe intensity), or by the profile of associated symptoms (i.e. nausea, vomiting, discomfort to light or sound, visual symptoms or other aura), or both. The frequency of other headaches should be limited to 6 days per month.

Unless otherwise justified, patients entered into adult studies should be above 18 years of age (for studies in children, adolescents and elderly (see 3.3.1 and 3.3.2). Both male and female patients are acceptable. Specific studies should be performed in children and adolescents (see Section 3.3.1).

Patients included should generally have had migraine for at least 1 year and there should be a 3-months well-documented retrospective history. Age at onset of migraine should be less than 50 years. The onset of headache at the age of 50 years or over is more likely to be the result of an underlying pathological condition that may resemble migraine than it is in younger patients. Acceptable and unacceptable concomitant therapy should be specified. Agents interfering with the test agent on a pharmacokinetic or pharmacodynamic level should be excluded.

Migraine sufferers attending specialist clinics may not be representative of the larger number of patients seen by primary care physicians. Neither group is likely to match those in the general population who usually do not seek medical advice. Clinical trials need to recruit widely in order to reflect the population who will use the agent when marketed. Early migraine trials may be conducted in specialist centres, but later studies should include patients from primary care or the community with as few restrictions as possible.

Acute migraine attack

A certain level of attack frequency, for instance one to six times per month, is necessary for inclusion. There should be at least 48 hours of freedom from headache between attacks of migraine. The frequency of other types of headache~~s~~ should not interfere with the assessments.

For patients with menstrual migraine (see section 3.3.3).

Where patients are using a prophylactic medication this should have remained unchanged for 3 months prior to inclusion. If prophylaxis has been withdrawn this should have been at least one month prior to inclusion or longer for compounds with long half-lives. If the study population incorporates patients with/without prophylaxis, the study population should be stratified accordingly. The use of rescue medication should be part of the protocol (see section 3.2).

Migraine prophylaxis

In order to justify migraine prophylaxis, attacks should occur at least 2 times per month, usually 2-6 times per month. There should be at least 48 hours of freedom from headache between attacks of migraine.

2. METHOD TO ASSESS EFFICACY

A continuous registration of the patients' migraine pattern during baseline and study period should be available.

The measurement scales used should be justified and validated for migraine [cf. also IHS Clinical Trials Subcommittee recommendations [3]].

The choice of secondary variables depends on the (secondary) study objectives and intended claims. It is recommended to pre-define the choice of secondary endpoints and their relative importance and account for multiplicity in the analyses.

Acute migraine attack trials

The recommended primary endpoint is the percent of patients pain-free at 2 hours after administration of the study agent. In migraine with aura treated during the aura period the same primary endpoint may be used.

Depending on the clinically relevant focus, secondary endpoints might be:

- The percentage of patients remaining pain-free defined as being pain-free at 2 hours with no use of rescue medication and no relapse within 48 hours after administration of the study agent.
- The incidence of relapse, defined as the return of headache of any severity within 48 hours after administration of the study agent when the patient was pain-free at 2 h after treatment (secondary treatment failure)[*].
- Efficacy on other migraine-associated symptoms: e.g. nausea, vomiting, photophobia and phonophobia [cf. IHS-classification].
- The intensity of headache at various time points.
- Headache relief: Percentage of patients with a decrease in headache from severe or moderate to mild or none at 2 hours.
- The time-to-meaningful relief.
- The speed of onset of action.
- The use of rescue medication.
- Global evaluation of medication by the patient.
- Functional disability at 2 hours and other time points.

In general the maintenance of the effect, relapses and effects on migraine-associated symptoms other than pain (e.g. nausea, vomiting, photophobia, phonophobia) at short-term are considered as important secondary endpoints.

The duration of attacks is not considered a reliable secondary endpoint as it is heavily influenced by the use of rescue medication, which is allowed after 2 hours.

Health-related quality of life (HRQOL) measures are not fully established in migraine, and their use is optional as one of the secondary endpoints.

Migraine prophylaxis trials

The recommended primary endpoint is the frequency of attacks within a pre-specified period, e.g., the mean frequency of attacks per 4 weeks or during the final 4 weeks of a 3-month study duration. The number of migraine attacks should be recorded irrespective of their duration, and the following rules should be used for distinguishing an attack of long duration from 2 attacks, or for distinguishing between attacks and relapses:

1. A migraine attack which is interrupted by sleep or temporarily remits, and then recurs within 48 hours after onset of the attack (or after administration of the study agent) should be recorded as one attack, and not two.
2. An attack primarily treated successfully with medication but with relapse within 48 hours counts as one attack.

[*] Previously, the term *recurrence* has been used, mostly defined as worsening of headache (to moderate or severe pain) within 24 hours of treatment and subsequent to headache response (mild or no pain)

Secondary endpoints might be:

- Responder rate where a "responder" is defined as a patient with a 50% or greater reduction in attack frequency during treatment compared to baseline.
- Number of days with migraine per 4 weeks.
- Intensity of headache averaged over attacks within an evaluation period.
- Speed of effect (active agents may be distinguished from each other or from placebo by how quickly reduction in attack frequency is achieved; thus, attack frequencies may be compared in the first 4 weeks or second 4 weeks of treatment).
- Drug consumption for acute treatment totalled over an evaluation period.

Headache indices multiplying frequency, intensity and/or duration are not recommended, as faulty weighting in the arbitrary numerical scores will be increased by multiplication and, most important, indices can in no meaningful way be compared between subjects. Furthermore, results are difficult to evaluate clinically.

The use of health-related quality of life (HRQOL) measures and Disability-adjusted life years (DALYs) is not established, and they should not be used until fully clinically validated.

3. STRATEGY AND DESIGN OF CLINICAL TRIALS

3.1 Early Studies in Man

Pharmacodynamics

There are no established specific pharmacological models of migraine. Studies should be performed in order to show both the action of the product on the serotonergic system and its vasoactivity on different vascular territories, and on other biological systems, as appropriate.

Early safety and efficacy studies should preferably exclude patients with other types of headache, alternatively, the patients should be able to distinguish between migraine and other types of headache.

In early (Phase II) efficacy trials parenteral therapy may be preferred if there is doubt about rapid bioavailability by the oral route. The optimal formulation should be studied before phase III trials.

Although preferred by most patients, oral administration is theoretically not the ideal mode of administration in acute migraine because absorption may be delayed by gastric stasis.

Alternative routes, especially in severely nauseated or vomiting patients (the injected, inhaled, sublingual, intranasal, transdermal, and rectal routes) may be explored.

Study designs should address agent administration both early in the attack and after the attack is fully *developed.*

Dose-Response Studies

Well-designed dose finding studies should be carried out in order to determine the dosage to be used in the confirmatory studies. Determination of plasma drug levels may be useful. If the dose(s) used in clinical trials differ from the clinically recommended dose(s), a justification must be given.

Pharmacokinetics

Pharmacokinetics of the proposed route of administration should be investigated both during migraine attacks and outside attacks because of possible differences in pharmacokinetics outside attacks and from volunteer studies.

Interactions

In general, pharmacokinetic interaction studies should be mechanistically driven. In case of other anti-migraine agents likely to be given simultaneously with the test agent in clinical practice, however, studies are advisable if an interaction cannot be excluded due to the pharmacokinetic properties of the product.

Also potential pharmacodynamic interaction with other agents (alcohol, vasoconstrictor drugs, oral contraceptives, anti-migraine drugs, and CNS drugs) should be considered.

3.2 Therapeutic Confirmatory Studies

Acute migraine attack trials

Pivotal trials should address both the efficacy in single migraine attacks and the consistency of the therapeutic response. Therefore, it is recommended that parallel-group studies on treatment of a single attack are supplemented with studies on treatment of several attacks ("consistency trials"), where e.g. one attack out of 5 is treated with placebo and 4 out of 5 attacks are treated with verum [3,4].

Treatment of relapse should also be investigated in a double-blind fashion. Such studies should have the same endpoints as described under II. Methods to assess efficacy, acute migraine attack trials.

It should be noticed that the headache is not a stable pain but develops gradually, or sometimes rapidly, to a peak with subsequent spontaneous resolution. This poses challenges regarding timing of intake of test medication, which might be early or when the attack is fully developed, and in evaluation of results. Additionally, within subjects there may be variability from attack to attack.

Study design

Controlled trials of acute treatment should be randomised, double-blind and placebo controlled. Three-arm trials are required for internal validation in active comparator studies because of the large and highly variable placebo effect in migraine studies. The choice of an active comparator should be clearly justified.

A 3-month well-documented retrospective history or a prospective baseline (run-in period) of at least one month is recommended both in order to determine the characteristics and the frequency of attacks per month. Treatment of acute attacks in this period is allowed, provided that any medication taken is reported.

Spontaneous attack rate may be highly variable. Treatment of an attack within a certain timeframe should be planned, i.e. if no attacks have occurred within a pre-specified period the patient should be withdrawn.

The observation period after the treatment of an attack should be at least 48 hours.

Use of rescue medication from 2 hours onwards should be part of the protocol.

Specific study designs (or specific trials) are needed to address the following situations:

- re-dosing of a study drug (in the same attack),
- tachyphylaxis.

In migraine with aura, specific studies may be performed to evaluate the action of the drug taken during the aura period. The time from onset of symptoms to treatment should be specified.

Statistics

The primary statistical estimate should concern the difference in percentage of patients who are pain-free at 2 h after taking study medication.

The statistical analyses may take into account migraine attacks with/without aura.

Consistency of effect over more attacks is to be the primary endpoint in appropriate trials and should be analysed for e.g. pain-free in at least 3 of 4 attacks treated with verum.

Sample size calculations should consider an adequate study population and subsequent analysis in 2- or 3-armed trials, as appropriate.

Migraine prophylaxis trials

In general, the subjective nature of migraine and a high placebo effect invalidate open and single blind trials. However, clinical observation may be hypothesis generating for possible prophylactic effect in migraine.

The superiority of the test agent in comparison with placebo should be convincingly demonstrated in randomised, 2-armed double blind controlled parallel group prophylactic trials. If justified, however, cross-over studies may be used, e.g. in proof-of-concept trials. Parallel group studies with 3 treatment arms with active comparator and placebo are recommended for internal validation because of the large and highly variable placebo effect in prophylactic migraine studies. Alternatively, the therapeutic efficacy may be tested in superiority trials against a well-established comparator. However, if the test agent is not better than the comparator non-inferiority cannot be claimed due to the lack of a placebo arm as internal validation. A prospective baseline (run-in period) of at least one month and a 3-month well-documented retrospective history is recommended in order to determine the characteristics and the frequency of attacks per month. Randomisation should occur after the run-in (baseline) period. Treatment periods should be at least 3 months after the titration period (if any). Continued observation beyond the treatment period for continuing efficacy is essential. Patients should be followed for at least 4 weeks after termination of the treatment period to detect possible rebound phenomena.

Appropriate acute therapy must be allowed for individual attacks. Patients can use their usual symptomatic or acute treatment provided that it can be safely administered with the study medication. Such treatment should not be changed during the trial. Other agents used for migraine prophylaxis should be discontinued at least 3 months prior to the trial.

Statistics

Stratification for baseline attack rate (e.g. > 3 or < 3 per 4 weeks) is recommended as the extent of the prophylactic effect might vary depending on this variable. Analysis of the efficacy for the entire treatment period, as well as for the specified period corresponding to the recommended primary endpoint (e.g. the mean frequency of attacks per 4 weeks or the final 4 weeks, see section II) should be employed.

3.3 Studies in special population

3.3.1 Children and adolescents

Due to different disease characteristics in children/adolescents and adults, the results of studies in acute/prophylactic treatment of migraine in adults cannot be extrapolated to children/adolescents. Specific studies in these age groups are therefore requested. See annex on clinical investigation in children and adolescents.

3.3.2 Elderly

Specific studies may be needed for the population over 65 years because of cerebrovascular diseases and other illness in this category of patients. However, both in acute and prophylactic migraine therapy, PK and safety data may be sufficient in elderly patients suffering from migraine for many years. In different elderly patient populations other data from proper clinical studies may be necessary. In elderly patients with recent onset of migraine, symptomatic disease should be excluded.

3.3.3 Menstrual migraine

The following statements are applicable to investigational drugs with specific claims on menstrual migraine, once efficacy/safety in non-menstrual migraine has been demonstrated.

Studies in menstrual migraine do have in principle the same design and endpoints as for studies in non-menstrual migraine. In studies in menstrual migraine the temporal relationship between menses and migraine attacks should be stringently recorded. For diagnostic purposes it is recommended to monitor this relationship for 3 cycles before entering the trial. In the acute treatment studies the percentage of patients sustained pain-free is an important secondary endpoint. In prophylaxis studies there is the option for peri-menstrual prophylactic treatment. The design of the prophylactic study should allow evaluating the possibility that attacks are merely postponed to a later time in the menstrual cycle.

Subgroups of patients with menstrual migraine from different studies in the clinical development plan may be combined in a meta-analysis if planned a-priori.

4. CLINICAL SAFETY EVALUATION

4.1 Specific adverse events to be monitored

Identified adverse events should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. Appropriate laboratory tests and cardiological recordings should supplement clinical observations.

All adverse events during the course of clinical trials should be fully documented with separate analysis of serious drug adverse events leading to withdrawal and patients who died while on therapy.

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self- poisoning should be provided.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of agent being investigated depending on the action on various receptors/pharmacodynamic properties.

Possible withdrawal effects after drug discontinuation should be evaluated. Development of tolerance should be assessed.

Specific attention should be given to the occurrence of agent overuse headache, which occurs after frequent use over time of acute medication for migraine (daily or almost daily usage depending on substance).

4.2 Extent of population exposure to assess clinical safety

The total clinical experience must generally include data on a large and representative group of patients.

4.3 Long-term safety

Migraine is a chronic condition and medication is likely to be used over long periods. An open study of at least 12 months duration should be performed in order to establish the long-term safety in both acute and prophylactic migraine treatment.

REFERENCES

1. Lauritzen M. Pathophysiology of the migraine aura: the spreading depression theory. Brain 1994; 117: 199-210.
2. International Headache Society Headache Classification Subcommittee. International classification of headache disorders, 2nd edition. Cephalalgia 2004; 24 (suppl 1).
3. International Headache Society Clinical Trial Subcommittee. Guidelines for controlled trials of drugs in migraine. Second edition. Cephalalgia 2000; 20: 765-786.
4. Goadsby PJ, Lipton RB, Ferrari MD. Migraine – current understanding and treatment. N Engl J Med 2002; (4)346:257-70.

ANNEX

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF MIGRAINE IN CHILDREN AND ADOLESCENTS

The prevalence of migraine with/without aura in children older than 6 years of age is 5 to 10%. Migraine with/without aura under 6 years of age is rare. Atypical migraine (e.g. abdominal migraine) which might occur in the younger age is out of the scope of this document.

Due to different disease characteristics in children/adolescents as compared to adults, the results of studies in acute and prophylactic treatment of migraine in adults cannot be extrapolated to children and adolescents. Moreover disease characteristics change with puberty. Therefore the efficacy of agent in acute or prophylactic treatment of migraine should be shown separately for children (6 - < 12 years age) and adolescents (12-18 years of age).

The development of a child friendly formulation (e.g., nasal drops, sublingual drops, sprays) is advocated. Bioequivalence studies are needed to show bioequivalence against the formulation used in the clinical studies.

The diagnostic criteria for migraine should conform to the state of art e.g. those of the International Headache Society (IHS). It is noted here that the definition of attack is different for pre-/post-pubertal subjects (i.e. <15 versus > 15 year), which has to be taken into account in prophylaxis studies.

Assessment of pain and other variables should be based on scales validated for migraine in these age categories e.g. VAS, categorical pain scales, behavioural scales. Assessment should be done by patients with/without assistance by the caregiver.

Acute treatment

A pharmacokinetic study may be needed in order to define the dose equivalent to the effective dose in adults.

As the consistency of effect has already been shown in the adult setting a single-attack study in both age categories is considered sufficient.

The single attack study should be randomised, double-blind, placebo-controlled and preferably active controlled (e.g. ibuprofen) with parallel group study design. Escape medication should be allowed.

Alternatively a cross-over trial may be considered where the treatment effect over several attacks is evaluated within one patient e.g. one attack out of 3 is treated with placebo and 2 out of 3 attacks are treated with the new agent or active control. It is noted that in the cross-over design the distinction between single attack studies and consistency studies disappears.

The study should have a run-in phase which may be from 2 to 12 weeks for an individual patient in order to increase the probability that an attack occurs during the study period. In addition the severity and duration of the attacks can be assessed.

Primary endpoint is identical to the one recommended in adults i.e., percent of patients pain-free at 2 hours after administration of the study agent. Secondary endpoints recommended are patients remaining pain-free or fall asleep at 2 hours with no use of rescue medication and no relapse within 48 hours after administration of the study agent, percentage subjects with partial relief (including children asleep at 2 hours, use of rescue medication, global evaluation by patient and/or parents, functional disability at 2 hours and other time points (e.g. behavioural scales). The evaluation of time to onset of effect is highly recommended.

Prophylaxis

In prophylaxis, studies should be randomised, placebo-controlled and preferably active controlled with a cross-over or parallel group design.

A run-in period is required. The duration of the trial depends on the attack rate at baseline which determines the likeliness that a decrease in attack rate, if present, can be shown over the period the double-blind observation last. See adult section.

Primary endpoint will be the frequency of attacks. In addition the speed of effect should be evaluated. Secondary endpoints may be the same as for the adult studies provided the assessment instruments are validated for migraine for these age groups.

It is known that cognitive behaviour therapy has a major impact on attack rate. Therefore, if applicable, either in the study design (i.e. stratification for CBT) and/or in the analyses this should be accounted for.

Safety

Long-term safety data are required (see ICH EI11 Clinical Investigation of Medicinal Products in the Paediatric Population).

Further especially for prophylactic treatment long-term safety data are required evaluating the impact of treatment on growth, endocrine development. In addition, if in the RCT the safety profile indicates an effect cognitive function (e.g., sedation, attention), long-term safety data on cognitive function may be needed.