European Medicines Agency

London, 24 January 2007

Doc. Ref. EMEA/CHMP/EWP/21477/2007

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF MIGRAINE

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	EFPIA	

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

GENERAL COMMENTS

Studies in paediatric / adolescent migraine patients have shown very high placebo response rates. While the placebo response in the adult population is typically in a range around 35%, in paediatric / adolescent trials placebo response rates of 50% or even higher were demonstrated. Consequently, from a statistical methodological point of view, it is very challenging to show efficacy of an active compound in this clinical setting. Not surprisingly, a number of migraine compounds, known to be effective in adults, have failed in paediatric / adolescent studies.

One reason for the high observed placebo rate in children / adolescents may be the comparatively shorter duration of the migraine attack. While migraine attacks in adults take 4 to 72 hours, paediatric migraine attacks usually take only between 1 and 48 hours. The experience from migraine trials in children / adolescents is that they often wait for a considerable time before they treat the respective attack. However, a time delay to treatment may bias a paediatric / adolescent study such that migraine attacks in children / adolescents may already resolve spontaneously according to natural history hereby inflating the "response rate", making it more difficult for an active treatment to separate from placebo.

One way out of this dilemma may be to introduce the "early intervention" concept, like it is advised for adults. In this setting patients who typically suffer from moderate to severe headaches would be included in the study, but instead of waiting until the migraine attack is fully developed these patients would be asked to treat a migraine attack early, while pain is still mild. This strategy could have the advantage that the natural resolution of the attack would not interfere with treatment effects and hence a separation of active vs. placebo would be more likely. A statement by the EMEA regarding the acceptability of this proposed "early intervention" paradigm would be highly appreciated.

Rapporteur's comment:
The suggestion that the high placebo response is responsible for the lack of efficacy is not agreed. The high placebo response is not an incidental observation but consistent over the controlled studies. Responses on active treatment are also high. Alternative explanation for this high response may different response characteristics of migraine in adolescent as compared to adults, larger heterogeneity of subjects included in the study etc. Hence the high placebo response forms not an explanation for not showing efficacy. Instead it should be subject of further investigation. The shorter duration of the attack and the tendency to wait longer before taking treatment as described may also indicate that migraine may be less severe in most children/adolescents as compared to adults. One may even question whether there is a need to treat an acute attack if the attack is already over in most patients when treatment will be started. At least this point at the heterogeneity of the migraine in these age groups. The early intervention concept is not new.

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
EFPIA ***Paragraph 2 & 7 p.11/12*** The requirement to study migraine in children rather than extrapolate from adults is reasonable. However, the guidance is unclear as to whether a single study including both age groups (6-12 and 12-18) is sufficient, or whether a study in each age group would be required. In paragraph 2 the guidance states efficacy must be shown separately in the age groups, whereas in paragraph 7 it states a single study in both age categories is considered sufficient (a statement which is in itself ambiguous). Separate studies in these age groups would be burdensome and would expose many children to investigational therapy unnecessarily. The aetiology of migraine in older and younger children is identical and the manifestations are very similar. *Proposed change* *An alternative would be to allow stratified randomisation based on the two age strata with a defined percentage below age 12 (25-30%). Subgroup analyses as a secondary endpoint should suffice to assess whether a difference exists in the responsiveness of the age groups.*	*The rationale of the categorisation is that, as stated, migraine characteristics are different before and after puberty. Thus efficacy should be shown separately in each age category.* *Whether this is done in two studies or in one study with separated subgroup analyses is not an issue. However, in a stratified study significance should be shown in both subgroups if both indications are opted for. There might be a multiplicity issue as well.* *Thus there is no ambiguity.* *Of note single attack study refers to one attack not to a single study. This may be stated more clearly. See later.*	The prevalence of common/classical migraine in children older than 6 years of age is 5 to 10%. Classical/common migraine 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 annex. 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 agents 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. A pharmacokinetic study is needed in order to define the appropriate dose. It is recommended to implement paediatric studies in the clinical development plan after a benefit in adult studies has been shown although these studies might be performed as a post marketing commitment (see ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population). 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

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
		attack is different for pre-pubertal /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 Comments p.11/12 There is no mention of whether study designs should address agent administration both early in the attack ('early intervention') and after the attack is fully developed (as for adults). Proposed change: Clarification needed.	*This depends on the claims already approved for adults.* No clarification is deemed necessary.	Acute treatment As the consistency of effect has already been shown in the adult setting, a **single-attack** ~~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 5 is treated with placebo and 4 out of 5 attacks are treated with the new agent or active control. It is noted that in such cross-over design the distinction between single attack studies and consistency studies disappears.

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
Acute Treatment Paragraph 4 p.11/12 It is not clear whether the referred to '*run-in phase'* is untreated or placebo treated. Furthermore the purpose of the run-in phase is not clear if historical data on attack frequency are available. *Proposed change: Clarification needed*	*The purpose of the run-in phase is to evaluate of the attack rate in order to increase the probability that a patient included will have an attack in the time interval of observation. Retrospective data are unreliable in this respect. Placebo run-in / untreated run-in is not an issue here. The issue is to increase the efficiency / sensitivity of the trial.* Furthermore, the 2-hour time point could lead to elevated placebo response rates in clinical studies. *No clarification is deemed necessary.*	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.

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
Acute Treatment Paragraph 5 Lines 1-2 p11/12 Given the fact that duration of headache pain is shorter in adolescents than in adults, the 2-hour time point for headache response and pain-free rates are not appropriate for migraine clinical trials conducted in an adolescent population. Reference: *Rothner, A. D., Wasiewski, W., Winner, P., Lewis, D., Stankowski, J., Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents, Headache 2006; 46: 101-109.* Furthermore, the 2-hour time point could lead to elevated placebo response rates in clinical studies. *Proposed change:* *"Primary endpoint is percent of patients sustained* pain free at 1 hour after administration of the study agent".* *see next comment	*This position has been unanimously challenged in the expert group consulted. It was explicitly stated that also in adolescents and children the primary en point should be the percent of patients pain-free at 2 hours after administration of the study agent.* *This was reinforced by a large clinical trial performed in migraine in adolescents where an effect was observed at 2 hours but not at one hour which was the primary endpoint.* *No changes are deemed necessary.*	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 falling asleep at 2 hours with no use of rescue medication and no relapse within 48 hour 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 h and other time points (e.g. behavioural scales). The evaluation of time to onset of effect is highly recommended.

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
Acute Treatment Paragraph 5 Lines 1-2 p.11/12 *'% of patients pain free at 2 hrs'* should be *'% of patients **sustained** pain free at 2 hrs*'. This is then consistent with section 3.3.3. (menstrual migraine) of the adult section *Proposed change: Amend as proposed.*	*Menstrual migraine is not representative for' common / classical migraine. Moreover sustained pain free is mentioned as secondary endpoint not as primary endpoint which should be (as stated as well) the same in menstrual migraine as for common / classical migraine.* *No changes are deemed necessary.*	
Acute Treatment Paragraph 5 Lines 2p.11/12 A secondary endpoint of '*patients falling asleep at 2 hours'* is mentioned. This could potentially mean that a highly sedating agent has a better response than a non-sedating agent even if the latter has better pain relief. Further to this point, the recommendations do not state how to handle patients falling asleep for the primary assessment (% of patients sustained pain free at 2 hours) *Proposed change: Clarification needed.*	*Clarification needed.* *For patients falling asleep within 2 hours pain freedomness cannot be assessed. So they should be categorised as non-responders.* *Highly sedating agent will make the trial insensitive to show an effect on the primary endpoint.* *No changes are deemed necessary.*	
Acute Treatment Paragraph 5 Lines 6 p.11/12 '*Functional disability'* should be further defined, e.g. according to a specific scale or response criteria. *Proposed change: Further definition needed.*	*Point is more that if an effect on functional disability is claimed this should be proven. How this is done, how this is measured, and whether the scale used and results are valid is part of the assessment.* *No changes are deemed necessary.*	

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
Prophylaxis Paragraph 1 p.11/12 In the discussion on prophylactic therapy, the draft states that the treatment for acute therapy should be optimalised (sic). In practice, this approach would be very difficult for investigators, would lengthen enrolment periods, and would subject children to needlessly long periods where their acute therapy is adjusted prior to entry into a study. *Proposed change* *The criterion for entry into a study of prophylaxis of migraine should be paediatric subjects who require prophylaxis or who have continued migraines despite prophylactic therapy. Adjustment of acute therapies should also be allowed during the course of a trial as migraine frequencies can be assessed whether or not their acute therapy is optimal.*	*The comment is correct as this does not influence the primary endpoint in prophylaxis studies, i.e. attack frequency.*	Prophylaxis In prophylaxis, studies should be randomised placebo controlled and preferably active controlled with a cross-over or parallel group design. ~~The treatment for acute attacks should have been optimalised before entry.~~
Prophylaxis Paragraph 2 p.12/12 The sentence *'The duration of the trial depends on the attack rate at baseline.....*' is vague and therefore provides limited guidance to Industry. *Proposed change* *Clarification needed, or a cross referral to the relevant adult part of the guideline.*	*The reason is clearly explained in the text.* *See changes as indicated.*	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**.

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
Prophylaxis Paragraph 4 p.12/12 At least one reference needs to be given in the reference list to support this statement *"It is known that cognitive behaviour therapy has a major impact on attack rate"*. There is little reference to CBT in the adult section of the guideline. With a randomised design, it would be expected that the proportions of patients with/without CBT would be similar across treatment groups, so mandatory need to account for this is unnecessary. *Proposed change* *Rewriting of the sentence (proposed text underlined): "It is known that cognitive behaviour therapy has a major impact on attack rate. Therefore, it may be necessary to account for this, either in the study design (i.e. stratification for CBT) and/or in the analyse".*	*CBT is more applied in children as in adults, thus more an issue here.* *See changes as indicated.*	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 ~~CTB~~ **CBT**) and/or in the analyses here should be accounted for.
Prophylaxis Paragraph 4p.12/12 The final sentence starting '*Therefore either in the study design….*' does not read correctly. *Proposed change* *Rewriting of the sentence as proposed above. In addition 'CTB' should read 'CBT'*	*See changes as indicated.*	

GUIDELINE SECTION TITLE: ANNEX		
Comment, rationale, proposed *changes*	**Comments rapporteur**	**Original text with amendments (in blue) proposed by rapporteur**
Safety Paragraph 1p.12/12 The guidance recommends long-term safety data with a focus on growth, development and cognition. Since many medicines are established in other indications prior to their testing in migraine, it would be helpful to clarify if long-term safety in another indication may be used in lieu of a long-term study in children with migraine, again, to minimize the unnecessary exposure of children to investigational therapies.	*The lack of such studies may indeed be justified by this. However, that is part of the assessment.* *No changes are deemed necessary.*	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 and cognitive function.