European Medicines Agency

London, 18 October 2006
Doc. Ref. EMEA/CHMP/EWP/392476/2006

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS

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

	Name of Organisation or individual	Country
1	G.J.Tijhuis and Nederlandse Vereniging voor Rheumatologie	NL
2	EFPIA	
3	Hoffmann-La Roche	

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
This guideline is welcome as it addresses the specific field of clinical trials in Paediatrics in view of long-term treatments. As a general remark, to improve readability we suggest that definitions are given where terms such as IL-1ra, IL-6, CTLA4ig are used as well as for all acronyms and abbreviations.(2) *Outcome: Abbreviations will be explained throughout the text*		
Foreword		
Last paragraph: *This guideline is intended to assists applicants during the development of medicinal products. It is only guidance; any deviation from guidelines should be explained and discussed in the Expert reports/Clinical Overview.* ***"Expert reports":*** Reference to Expert reports is not warranted as the CTD is the mandatory format to submit an application: In the CTD format the clinical overview replaced the Expert reports. (2) *Outcome:* *Accepted*		
1. INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
General information	We question whether JIA is the most common systemic autoimmune disease in children and adolescents and therefore suggest the following change: ***With an annual incidence of 0.008 - 0.226 and a prevalence of 0.07 - 4.01/1000 children JIA is less common than rheumatoid arthritis (RA) in adults but it is* one of *the most common systemic autoimmune disease in children and adolescents.*** (2)	accepted ***With an annual incidence of 0.008 - 0.226 and a prevalence of 0.07 - 4.01/1000 children JIA is less common than rheumatoid arthritis (RA) in adults but it is* one of *the most common systemic autoimmune diseases in children and adolescents.***
	The introduction of anti-Tumour-Necrosis-Factor- α(TNF- α) therapy, *appeared to* have a clinically relevant impact on the outcome of patients with polyarticular JIA who were unresponsive to methotrexate Use of **'appeared'** suggests that this is no longer the case. We suggest that ***'appears'*** be used. (2)	accepted
	This statement is incorrect. Whilst patients with a polyarticular presentation were included in the studies, the patient populations	Results of a multicentre paediatric trial performed in the US demonstrated

	included several sub-types, not just polyarticular JIA. The use of an anti-Tumour-Necrosis-Factor-α (TNF-α) in those JIA patients with polyarticular course (which included a number of subgroups of JIA) appears to be more beneficial in some subgroups than others (Quartier, P, Taupin, P, Bourdeaut, F et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to onset type. Arthritis and Rheum 2003; 48(4):1093-101).	that etanercept was effective and well-tolerated in 74% of children (n=69) with JRA and active polyarthritis, regardless of the type of disease onset which included pauciarticular (10%), polyarticular (58%) and systemic (32%) type of onset. (Ref. 16) As a consequence etanercept has been licensed for "the treatment of active **polyarticular-course juvenile chronic arthritis** in children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate." There is evidence that in active systemic onset JIA this treatment is less effective with a response only in a minority of patients (Ref 18 and Takei S et al: Safety and Efficacy of high dose Etanercept in treatment of juvenile rheumatoid arthritis. J Rheumatol 2001; 28: 1677-80; Kumra Y et al: Use of etanercept in the treatment of systemic JIA in the USA results o f survey. Ann Rheum Dis 2000, 59:741). In some of the publications the JRA classification was used which brings some uncertainty in relation to the JIA classification since there are gaps and overlaps among these classification systems. Therefore wording is: **The introduction of therapy with tumour necrosis factor receptor (p75):Fc fusion protein (etanercept), *appears to* have a clinically relevant impact on the outcome of patients with active polyarticular disease (which includes several types of onset) and who are unresponsive to methotrexate.**
Second paragraph of page 4/9 last sentence	The phrase "*Treatment with other medicinal products such as infliximab, adalimumab,…*" suggests that these products are not anti-TNF therapies, when they are. (2)	Treatment with other medicinal products such as different types of TNF modulators, Interleukin-1 ra (Interleukin-1 receptor antagonist), anti-IL-6 receptor (anti- interleukin 6 receptor) and CTLA4ig (cytotoxic T-lymphocyte antigen) are currently under clinical investigation in trials suitable to fulfil regulatory requirements.
Scope last paragraph	*In comparison to adults there are as well pharmacokinetic and phamacodynamic differences, impacts on growth and development and differences in perception of disease depending on cognitive levels in different age groups."* It may be reasonable to add here that the most common JIA subtype, oligoarthritis, may persist, evolve or resolve, i.e., show "***spontaneous remission*** (2)	The course of JIA often includes periods of remission and exacerbation, which require very different treatments. Disease duration is unpredictable but, in the majority of cases, JIA goes into spontaneous remission. In comparison to adults there are…. Apart from that insertion of the following addition to the introduction (page 4/1):

2nd sentence third paragraph	The second sentence of the third paragraph states "Extrapolation from efficacy results in adult RA is inappropriate since JIA represents a complex group of diseases divided into several categories with different prognoses and variable clinical presentations within the paediatric population." Whilst it is certainly true that extrapolation of adult RA efficacy results to systemic JIA is inappropriate, the same should not be said of polyarticular JIA. The statement should be tempered to represent cases where extrapolation of adult RA efficacy data may be appropriate. (3)	The prognosis depends on the clinical category of JIA, its severity, the time point of initiation of therapy and adequacy of treatment. *This is not correct.* We are of the opinion – and this was extensively discussed during previous EWP meetings- that in **most** of the cases (not only systemic subtype) it is inappropriate to extrapolate efficacy results from RA to JIA. The presence or absence of rheumatoid factor (RF) allows for polyarticular JIA to be distinguished into two subforms: RF negative and RF positive. RF positive polyarticular JIA is rare in children (<5% of all JIA patients) and is considered the equivalent of adult RF positive rheumatoid arthritis. RF negative polyarticular JIA accounts for 15-20% of all JIA cases is a complex form, which probably includes different diseases. The variable course and eventual outcome of the disease in different patients reflect this complexity and we do not agree that for this subtype efficacy results from adult RA can be extrapolated. The oligoarticular subtype with early onset represents about 50 % of JIA cases and is not observed in adults at all. Systemic arthritis (less than 10%) is characteristic of children and is seldom observed in adults. (www.pediatric-rheumatology.printo.it) The following addition to the sentence was inserted: "Extrapolation from efficacy results in adult RA is **mostly** inappropriate since JIA represents a complex group of diseases divided into several categories with different prognoses and variable clinical presentations within the paediatric population. The polyarticular RF positive category which accounts for less than 5% of cases of JIA may be an exception since it is currently regarded as early onset RF positive RA."

Patient Characteristics and Selection of Patients		
Line no. + para no.	**Comment and Rationale**	**Outcome**
1st paragraph page 4/9	*A paediatric investigation plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy in all of the paediatric population that may be concerned by the medicinal product."* As it refers to the New European Paediatric Legislation, this paragraph should be moved in the section "General Information". (2)	Accepted. The paragraph is moved to the chapter "Scope" of the "General Information".
3rd paragraph page 4 /9	*The efficacy of the agents should be evaluated by subtype to reflect the potential differences in response among the categories distinguished by the ILAR criteria. Patients should be grouped appropriately based on common practice and history of responsiveness of disease to particular types of agent. However, selection of patients should not be overly restrictive either. A study combining patients from multiple categories could be appropriate for categories in which patient numbers are limited. The systemic form should always be studied separately if a claim in this category is to be made."* ➢ Limited patient numbers coupled with a paediatric target population will reduce the opportunity to conduct meaningful, adequately powered studies in some subtypes. In order to overcome this problem, it is proposed that a study combining patients from several categories may be justified, with the exception of systemic arthritis. However, this raises a couple of points which require further clarification: ➢ The guideline is unclear with respect to the subtypes studied in clinical trials and the indications that will appear on the marketing authorization. Will studies in all subtypes be required to obtain an indication for JIA? If all subtypes must be represented for a claim in JIA, then the guideline should be clarified to reflect this fact.	Yes. A general indication JIA can only be obtained if efficacy in all subtypes is proven. Otherwise the indication has to be specified as was already done in recent marketing authorisations: e.g. Etanercept: "Treatment of active polyarticular course juvenile chronic arthritis in

	➢ The guideline should address the treatment of clinical studies, which have been initiated prior to the issue of this draft guideline and without the proposed break down by subtype. Given that JIA is a rare disease in a paediatric population, and that the target patient population is therefore small, retrospective application of this guideline could discourage further research. (2)	children aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of methotrexate." or Methothotrexate (Metoject): "Polyarthritic forms of severe, active juvenile idiopathic arthritis when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate." The paragraph reads: Efficacy cannot be projected from adults with the exception of RF-positive polyarthritis. Therefore a general claim for the indication JIA can only be obtained if efficacy is shown for all categories. The systemic form should always be studied separately if a claim in this category is to be made. Considering the rarity of some subtypes a heterogeneous study population may be justified but a positive treatment effect should still be demonstrated in each subgroup. The efficacy of the agents should be evaluated by subtype to reflect the potential differences in response among the categories distinguished by the ILAR criteria, unless alternative criteria are adequately justified. We are not aware of the fact that any guideline addresses the treatment of clinical studies prior to its issue.
p 5 last sentence	The third paragraph begins with the sentence "The efficacy of the agents should be evaluated by subtype to reflect the potential differences in response among the categories distinguished by the ILAR criteria." To be consistent with the 6th paragraph of the General Information section of the Introduction the sentence should state "The efficacy of the agents should be evaluated by subtype to reflect the potential differences in response among the categories distinguished by the ILAR criteria, **unless alternative criteria are adequately justified**." (3)	see above
page 5	**3. Method to assess efficacy**	
	The definition of remission should be used in addition to the JRA 30 once defined as primary endpoint. However it is still being worked out, as the last consensus conference did not reach consensus" The document is asking for use of "remission" as a primary endpoint	The first sentence clearly says "The definition of remission should be used in addition to the JRA 30 **once defined** as primary endpoint." After discussion during EWP meetings it was decided to include this part since it would be reasonable to have this endpoint as a reflection of the ultimate goal of JIA treatment that would preclude later changes of the guideline.

	despite the lack of a consensus definition. We assume that until consensus is reached, this can be open to discussion otherwise we suggest deletion of the sentences until consensus is reached. (2) It is not reasonable to require that a remission definition be used if there is not a consensus on its definition. With the acceptance of a definition of consensus this requirement can be met, at this point it cannot. Therefore, the deletion of this statement is proposed. (3)	To clarify the wording is: The definition of remission is still being worked out. However, once defined it should be used in addition to the JRA 30 as primary endpoint.
	Depending of the pharmacological rationale of the treatment studied relief of pain should be primary endpoint in the overall evaluation of efficacy". We suggest as follows to modify to improve clarity: *"Depending* **on** *the pharmacological rationale of the treatment studied**,** relief of pain should be* **a** *primary endpoint in the overall evaluation of efficacy"* (2)	The following was decided: Depending on the pharmacological rationale of the treatment studied, relief of pain should be a co-primary endpoint in the overall evaluation of efficacy.
	In the same paragraph, we also suggest to change *"Clinical manifestations like morning stiffness and pain are probably as often encountered in JIA as in adult disease, however children may communicate symptoms more indirectly which makes careful observation and questioning of, the parent necessary"* (2) to *"Clinical manifestations like morning stiffness and pain are probably as often encountered in JIA as in adult disease, however children may communicate symptoms more indirectly which makes careful observation* **by,** *and questioning of, the parent necessary"*	Children may communicate symptoms more indirectly, which makes careful observation and questioning of children by their parent(s) necessary.
	The third paragraph begins "A composite score can be a better representation…" This paragraph is confusing as written. It should be made clear that the expectation to demonstrate clinical relevance of a composite score is only expected of ***new*** composite scores that have not yet been validated. For the criteria developed by PRINTO, which are referred to in the first paragraph, this requirement presumably does not apply. (3)	Has been omitted
	The fifth paragraph begins "The JRA 30 reflects those signs and	

	symptoms accepted for the evaluation of RA, though…". It is not true that JRA 30 reflects those signs and symptoms accepted for the evaluation of RA, as there are additional variables specific to juvenile arthritis included in that composite end-point. The sentence should read "The JRA 30 reflects those signs and symptoms accepted for the evaluation of **JIA**, though…" (3) Additionally, unless there is agreement on a validated pain score to be used in all paediatric arthritis studies the requirement for a pain score as a primary endpoint in studies in all sub-types should not be included. Furthermore, it has been shown by Kuis *et. al.* that there is an inverse relationship between indices of disease activity and the pain threshold. Indeed, they suggest that active joint count, swollen joint count, VAS and functional CHAQ (components of the JIA 30) and pain threshold are inversely correlated; indeed when patients with juvenile arthritis had actively inflamed joints the pain threshold was reduced by 31%. This appears not to carry over to pain VAS which may measure different aspects of pain. It is not clear how pain measurement (once a standardized method is determined) would change with different subsets of JIA, different age groups, duration of disease, gender etc. and there would need to be standardized for each subset before being required, since pain seems to be more dominant in systemic and severe polyarticular disease than oligoarticular forms of the disease. (Kuis W, C J Heijnen, J A Hogewen, G Sinnema, P J Helders How painful is chronic arthritis? Arch Dis Child 1997(5); 77:451-453). Therefore, whilst the importance of assessment of pain for some sub-sets should be stressed, the requirement for a pain relief primary end-point should not be included. (3)	accepted For a symptom modifying anti-rheumatic drug such as NSAIDS or COX-2 inhibitors pain assessment is an important endpoint and should therefore be measured as primary endpoint. This would be in accordance with the CHMP guidance CPMP/EWP/556/95 Points to consider on clinical investigation of medicinal products for the treatment of rheumatoid arthritis (although this does not focus on children) that suggests that primary efficacy measures have to be chosen adequately depending on the pharmacological rationale of the treatment studied. For symptom modifying anti-rheumatic drugs these are usually pain and physical function. The JRA 30 was originally developed for assessing efficacy of DMARDs and physical function is a core component whereas a component of pain is not included. The paper clearly states that **appropriate rating scales have to be chosen according to age and justified by the applicant** (*VAS for older children above 5, e.g. facial expression scale in younger children*). The paragraph is kept with a modification: Depending on the pharmacological rationale of the treatment studied, relief of pain should be a co-primary endpoint in the overall evaluation of efficacy.
	4.1.2. Dose response studies	
	The assessor would like to include or refer to the following text of the guideline ICH Topic E11 Clinical investigations of medicinal products in the paediatric population (CHMP/ICH/2711/99) that states that when the medicinal product is to be used in the paediatric population for the same indications as those studied and approved in adults, the disease process is similar in adults and paediatric patients, in such cases pharmacokinetic studies in paediatrics together with safety studies may	Well-planned dose ranging studies should be carried out before the confirmatory clinical trials are undertaken following existing guidelines. The aim is to develop dosing recommendations that will ensure that the patients will obtain treatment that is effective and safe. A dose range for the assessment of dose-response in children should be based on recommended doses in adults of an appropriate pharmacokinetic

	provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults. Further no comments. (1)	parameter, most commonly AUC for chronic dosing in patients. In those cases where the disease process is similar in adults and paediatric patients (i.e. in patients with RF-positive polyarthritis), pharmacokinetic studies in paediatric patients together with safety studies might provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults (see ICH E11).
	4.1.3 Interactions	
	"Whenever patients use anti-rheumatic therapy other than the one studied interaction studies have to be performed" Some classes of therapeutic agents are unlikely to have a PK effect on another, e.g., biologic agents and so we suggest the following change: Whenever patients use anti-rheumatic therapy other than the one studied, interaction studies should be considered ~~have to be performed~~. (2)	accepted
	4.2.1.Study design	
	"Like in adult RA in this disease only the parallel group design is acceptable as a means of assessing efficacy and safety". It has been noted in this document that JIA is a compilation of arthritides. It is therefore inconsistent to use the phrase, **'***this disease'***.** The reading of the sentence would also be improved to increase clarity We suggest: ~~*Like in adult RAZ in this disease only*~~ *The parallel group design is the only acceptable means of assessing efficacy and safety.* (2) *"In order to explore the degree to which treatment effects are sustained in the long-term, a study design may be employed in which efficacy measures are observed after randomised and blinded withdrawal from a long period of treatment."* It is noted in section 2.4, 'Study Duration', that a blinded withdrawal design may also be used for primary demonstration of efficacy. Reference to this could be made here. We also suggest that **'from a long period of treatment'** is unnecessary and should be deleted. (2)	The parallel group design is the only acceptable means of assessing efficacy and safety. In order to explore the degree to which treatment effects are sustained in the long-term, a study design may be employed in which efficacy measures are observed after randomised and blinded withdrawal (see 4.2.3.4.).

	The fifth paragraph contains the sentence, "Alternatively to the latter design, a three arm study where patients receive, additionally to established active treatment, either the new agent or another established comparator or placebo…" The suggested design including combination of two active comparators with unknown efficacy and safety when used in combination is not appropriate. Also, according to the CHMP position paper on the role of active comparator studies (EMEA/119319/04), the role of such studies is not to position a product in the treatment paradigm. The sentence should therefore be truncated to, "Alternatively a three arm study design (verum, active comparator, placebo) may be considered." (3)	
	4.2.2. Target population	
penultimate paragraph	*Other treatment modalities interfering with study treatment are of particular importance. Careful registration for example of concomitant non-pharmacological treatment (physical therapy of various types etc.) has to be performed and medication for diseases other than rheumatic disease must be completely documented.* For clarity we suggest the following changes: *Other treatment modalities interfering with study treatment are of particular importance.* ~~*Careful registration for example of*~~ *Concomitant non-pharmacological treatment, (physical therapy of various types etc.)* ~~*has to be performed*~~ *, and medication for diseases other than rheumatic disease must be completely documented* (2) The first sentence of the third paragraph includes the term "childhood chronic arthritis". We should replace "childhood chronic arthritis" with JIA, in order to maintain consistent terminology. (3)	accepted accepted
	4.2.3.2.Established comparator	
	The second paragraph begins, "The need for a comparator is determined by the intended therapeutic position of the product…" According to the CHMP position paper on the role of active comparator studies (EMEA/119319/04), the role of such studies is not to position a product in the treatment paradigm. (3)	accepted

	4.2.3.4. Study duration	
	"Where data in the adult population are available and are consistent with the profile observed in paediatric patients, it would appear to be unnecessary and potentially unethical, to require a large efficacy and safety database, including data from long-term exposure, to be provided for paediatric patients." For clarity, the phrase "*at the time of submission of the marketing authorisation*" should be inserted i.e. "*Where data in the adult population are available and are consistent with the profile observed in paediatric patients, it appears unnecessary and potentially unethical, to require a large efficacy and safety database* ***at the time of submission of the marketing authorisation****, including data from long-term exposure, to be provided for paediatric patients."* (2) The required duration of phase III trials could be clarified as the draft guideline contains somewhat contradictory statements. The second sentence of the second paragraph of **section 2.4** notes "*For disease modifying therapies study duration of not less than 6 months is necessary.....Where data in the adult population are available and are consistent with the profile observed in paediatric patients, it would appear to be unnecessary and potentially* ***unethical, to require a large efficacy and safety database,*** *including data from long-term exposure, to be provided for paediatric patients."* This appears to contradict **section 5.3** which states *"To assess clinical safety and identify relevant adverse reactions an observation period of not less than twelve months is required. Taking into consideration the chronicity of the disease and the need for long term treatment longer periods may even be more appropriate.* (2)	accepted The duration of the placebo phase depends on the characteristics of the specific product. For symptomatic treatment (e.g. NSAIDs) 2 to 4 weeks is acceptable. Depending on the severity and the activity of the disease for disease modifying products a placebo phase of 6 weeks to three months may be needed. Anti-inflammatory effects, relief of symptoms such as pain or maintenance of symptomatic improvement should be evaluated for at least 4 and up to 12 weeks. For disease modifying therapies a study duration for evaluating maintenance of effect of at least 6 months is necessary. In case of positive efficacy data in adults 3 months studies are considered sufficient. Alternative study designs such as randomised withdrawal study design should be considered (see 4.2.1). in 5.3. it reads: Whenever there are no data in the adult population that are consistent with the profile observed in paediatric patients an observation period of

		not less than twelve months is required to assess clinical safety and identify relevant adverse reactions in the paediatric population. Taking into consideration the chronicity of the disease and the need for long-term treatment even longer periods may be necessary.
	5. Clinical Safety Evaluation	
5.1.	**1. Specific adverse events to be monitored** **Long-term data, either while patients are on chronic therapy or during the post-therapy period, are necessary to determine possible effects on skeletal, behavioural, cognitive, sexual and immune maturation and development.** This statement appears inconsistent with the last statement in section 2.4. Should the statement read as follows? **Post-study/post-authorisation *long-term data, either while patients are on chronic therapy or during the post-therapy period, are necessary to determine possible effects on skeletal, behavioural, cognitive, sexual and immune maturation and development*.** *(2)*	Accepted
5.3.	➢ *To assess clinical safety and identify relevant adverse reactions an observation period of not less than twelve months is required. Taking into consideration the chronicity of the disease and the need for longterm treatment longer periods may even be more appropriate.* It should be clarified that the long-term treatment referenced above is intended to mean post marketing studies. As the statement currently stands, it contradicts the statement in section 2.4 on study duration: "*Where data in the adult population are available and are consistent with the profile observed in paediatric patients, it would appear to be unnecessary and potentially unethical, to require a large efficacy and safety database, including data from long-term exposure, to be provided for paediatric patients*. For clarity we suggest: ***Taking into consideration the chronicity of the disease and the need for long term treatment,* even *longer periods may be appropriate.*** (2)	Whenever there are no data in the adult population that are consistent with the profile observed in paediatric patients an observation period of not less than twelve months is required to assess clinical safety and identify relevant adverse reactions in the paediatric population. Taking into consideration the chronicity of the disease and the need for long-term treatment even longer periods may be necessary.

	➢ *"The safety database should be supported by reference to available data on the use of the product in other indications (e.g. adult RA) and through extensive monitoring **of paediatric patients** in the post-marketing setting."* It is recommended that the phrase "***of paediatric patients"*** be inserted for clarity. It should also be specified that the post-marketing studies referred to are standard post-marketing surveillance studies and not post-marketing observational studies or registries. This section should also include cross-reference to the paediatric pharmacovigilence guideline. (2) This section does not appear to be consistent with the last paragraph of the study duration section of strategy and design of clinical trials. If it is unnecessary to require a large safety database including long-term exposure data, it does not seem reasonable to specify a twelve-month period of observation. This section should perhaps be qualified with respect to unmet need and the utility of data gained post-licensure. (3)	The safety database should be supported by reference to available data on the use of the product in other indications (e.g. adult RA) and through extensive monitoring of paediatric patients in the post-marketing setting. see above