European Medicines Agency

London, 24 January 2007
Doc. Ref. EMEA/CHMP/EWP/21568/2007

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INTENDED FOR THE TREATMENT OF NEUROPATHIC PAIN

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

	Name of Organisation or individual	Country
1	EFPIA	
2	Merck Sharp & Dohme	

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GENERAL COMMENTS

SPECIFIC COMMENTS ON TEXT		
III.3 Studies in special populations Children		
Comments, rationale, proposed changes	**Comments rapporteur**	**Text amendments proposed by rapporteur**
Section 3.3 Paragraph 2, p.9/10 (MSD) Delete text stating that pharmacokinetic data in children and adolescents are required for authorisation of drugs for neuropathic pain in adults. Please revise to state that the collection of such data is encouraged. **Section 3.3 Paragraph 2, p.9/10 (EFPIA)** We do not agree that "pharmacokinetic data in children and adolescents <u>will be required</u> for a medicinal product authorised for neuropathic pain in adults." As that there might be exceptions when pharmacokinetic data would not need to be provided in children and adolescents for a medicinal product authorised for neuropathic pain in adults. As indicated in the recently adopted Guideline on the role of pharmacokinetics in the development of Medicinal products in the paediatric population (EMEA/ CHMP/ EWP /147013/2004): "An application for paediatric use of a medicinal product should include sufficient information to establish efficacy and safety. Paediatric patients have the same right to well investigated therapies as adults. There are, however, several reasons why it is more difficult to study a medicinal product in paediatric patients, particularly in very young patients. Hence, it is often unrealistic to expect the applicant to fully demonstrate efficacy and safety in paediatric patients in clinical studies. In such a situation pharmacokinetic data may be used to extrapolate efficacy and/or safety from data obtained in adults or in paediatric age groups other than the age groups applied for."	*MSD is right the text could be read as if PK data in children and adolescents are required for authorisation of drugs for neuropathic pain in adults pre-approval. This was not intended. . The text is amended in accordingly.* *It is agreed that when sufficient information to demonstrate efficacy and safety in paediatric patients can not be obtained, this does it is not necessarily mean that PK data always should be generated for <u>each</u> age category. However, extrapolation implies that PK data that allow such extrapolation are available. The text is amended in accordingly.*	**III.3 Studies in special populations** **Children** There is very little information with regard to children and neuropathic pain. The more frequent neuropathic pain models in adult studies, i.e. post-herpetic, diabetic polyneuropathy and post-stroke pains are very rare in children. Neuropathic pain in children and adolescent represents a heterogeneous group of pain with various aetiologies. The more frequent are traumatic neuropathic pain, phantom pain, obstetrical brachio-plexus lesion and post anti-neoplastic treatment pain (e.g. vincristine). There is a lack of epidemiological data to estimate the prevalence of those pains in children, even if overall they are not very rare. Even without a full knowledge of maturation of the CNS, it is not expected that there is a difference in mechanism of neuropathic pain between adults and adolescents. In view of the heterogeneicity of neuropathic pain in children and adolescent, it is recognised that clinical development might be difficult. ~~Nevertheless, pharmacokinetic data in children and adolescent will be required for a medicinal product authorised for neuropathic pain in adults.~~ ***When sufficient information to demonstrate efficacy and safety in paediatric patients can not be obtained, pharmacokinetic data may form the bases of the dose recommendations in children, although it should be***

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We suggest reflecting this statement in this paragraph. The following re-wording of this paragraph is therefore proposed: *In view of the heterogeneicity of neuropathic pain in children and adolescents, it is recognised that clinical development might be difficult. When sufficient information to demonstrate efficacy and safety in paediatric patients could not be obtained in clinical studies, pharmacokinetic data may be used to extrapolate efficacy and/or safety from data obtained in adults or in paediatric age groups other than the age groups applied for.*		***properly justified.***
Section 3.3 Paragraph 2, p.9/10 (EFPIA) Consideration should be given to the use of population kinetics to obtain PK data rather than a formal PK study, to reduce the number of blood draws and to decrease the time in hospital for children. This also reduces the psychological burden that they are "sick" It is proposed to add at the end of the second paragraph: Consideration should be given to the use of population pharmacokinetic methods as a mechanism to obtain paediatric PK data rather than formal PK studies, in order to limit the period of hospitalisation and minimise the number of invasive procedures in individual children	*The validity of the PK data generated is part of the assessment procedure which includes the acceptance of data generated by population kinetics. There is no reason to mention explicit methods of PK data sampling in a non-PK guidance.*	
Section 3.3, Paragraph 3 p.9/10 (EFPIA) 1) Using the term 'common adult/children models' is ambiguous. We presume what is meant is 'models common to both adults and children', rather than models that are 'common' i.e. frequent. 2) It can be understood how study of a model such as	*It is agreed that the term 'common' is ambiguous. The text is adapted accordingly.* *If an effect in phantom pain has been shown in both*	Furthermore, investigation of efficacy of a product in ~~common adult/children~~ models **common to both adults and children** (e.g. phantom pain) ~~in adults and children~~ is encouraged **where possible** in order to better know how efficacy data can be extrapolated from adults to children or from one model to another.

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phantom pain in both adults and children could help in understanding extrapolation of data from adults to children, but it is not clear how it would help with extrapolation of data from one model to another.	*adults and children the assumption is that the responsiveness of the pathophysiological pathway by which the effect of the agent is mediated is alike. Hence it becomes more likely that the same holds for other models (bridging).*	
3) Realistically, given the under diagnosing of neuropathic pain (and the *relative* rarity of it anyway) in this age group, it would be very difficult to recruit these patients in any numbers where it would be able to derive a statistically significant answer in terms of efficacy. Additionally, the assessment of pain (both in terms of pain intensity and the multidimensional aspects of chronic pain) is clearly more challenging in children. It also depends on the age group being considered: 10-18 year olds are easier to assess than children younger than this. An alternative would be to recommend open label or cross-over designs for children with specific types of neuropathic pain. A statement such as 'It is acknowledged that a robust evaluation of efficacy in neuropathic pain in children is very difficult, unlikely to be possible etc' or something similar, would be helpful in this paragraph.	*It is not advocated to give up proper studies in advance. A small randomised control study is preferable above open label uncontrolled studies. Referred is to the NFG on small populations.*	
4) Listing other particular models beyond phantom pain for possible investigation in children would be helpful. The following re-wording of this paragraph is therefore proposed: *Furthermore investigation of efficacy of a product in models common to both adults and children (e.g. phantom pain) is encouraged, where possible, in order to better know how the efficacy data can be extrapolated from adults to children. However, since a robust*	*Phantom pain is just an example mentioned. More than one example raises discussion why others are not included as well.* *As is clear form the argumentation above the last sentence is not agreed.*	

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evaluation of efficacy in neuropathic pain in children is very difficult alternatives such as open label or cross-over designs for children with specific types of neuropathic pain may be considered.		