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Human Medicines Development and Evaluation

Paediatric Rheumatology Expert Group Meeting

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List of participants:

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Participation via teleconference:

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Conclusions

1. Chronic idiopathic arthritis should be used as the name of the condition for PIPs for medicines for juvenile idiopathic arthritis (JIA). This condition would include rheumatoid arthritis, psoriatic arthritis, and ankylosing spondyloarthritis in adults and juvenile idiopathic arthritis (JIA) in children. JIA includes the childhood equivalents of the above mentioned adult diseases as well as forms that are specific to children or that occur much more frequently in the paediatric age. Whenever development is considered in any of the three adult diseases, in principle a PIP is required for JIA.
2. Because there is a need for the treatment of children from the age of one year, particularly for systemic JIA as it occurs as early as in children younger than 2 years, a waiver should be granted generally only for children from birth to less than 1 year. However, based on the profile of the new medicinal product, a waiver could be possible for older children, based on case by case evaluation.
3. There are 4 target patient populations to be addressed in a development for JIA:
    a. Polyarticular course JIA (patients with history of involvement of more than 4 joints, no systemic JIA and no ERA)

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b. Oligoarticular course JIA (patients with history of involvement of no more than 4 joints, no systemic JIA and no ERA)

c. Systemic JIA (including both with and without active systemic features)

d. Enthesitis-related arthritis (ERA, as defined by ILAR criteria)

4. All 4 target populations should be discussed in each PIP for JIA with regards to possible benefit of the proposed treatment or prevention. Adequate measures must be proposed for those patient populations where the need has been identified. Individual clinical trials may allow merging of two or more target patient populations through specific inclusion/exclusion criteria, or may define the target patient population in more detail.

5. The definition of target patient populations for clinical trials must not prevent the study of the biological background of individual JIA subtypes; the evaluation of safety and efficacy in ILAR JIA subtypes must be proposed where feasible. Clinical trials should also be used as an opportunity to collect biological data on the background and treatment response in individual patients, and contribute to better understanding of the heterogeneity of the disease.

6. There is a concern on the long term impact of immunomodulating medicines, especially biologics targeting crucial molecules of the developing immune system in young children. The potential of non-clinical studies in juvenile animals in this respect is limited, and interpretation of their relevance for children with JIA is questionable. The response to immunisations needs to be studied in clinical trials. The issue requires further careful analysis before any model recommendation can be adopted.

7. Pharmacokinetic studies are an important part of the development, and have to be performed for all new active substances. Extrapolation of adult pharmacokinetic data is not possible. In most cases with immunoglobulin molecules PK study can be performed as the initial segment of an efficacy/safety trial. In small children and in systemic JIA separate dose-finding study may be necessary before the initiation of efficacy trials. Modelling and simulation is recommended to reduce sampling burden in children but it is recognised that data are scarce in this regard.

8. Different measures/study designs may be appropriate for the evaluation of efficacy and safety of new active substances, indications, pharmaceutical forms and routes of administration. A standard full development with placebo-controlled randomised efficacy trial is rarely possible, and alternative designs may be acceptable, for example randomised withdrawal designs; however efficacy in the primary population (open-label phase) should be stressed. The role and limits of extrapolation of efficacy need further discussion and must be addressed also within the framework of post-marketing requirements.

9. Post-marketing studies play a significant role in establishing the long-term safety and efficacy and treatment duration. Based on a case by case evaluation, these studies should be part of PIP or a follow-up measure. A European registry for patients treated with biologics (PharmaChild) is being established by the Paediatric Rheumatology European Society (PRES) in collaboration with the Paediatric Rheumatology European Society (PRINTO). The regulatory agencies are invited to have a closer co-operation in the establishing and steering of the registry.

10. The following safety concerns have been identified for biologics in treatment of JIA: infections, especially opportunistic infections, autoimmune diseases (including IBD, uveitis and demyelinisation), malignancies, macrophage activation syndromes (MAS), growth and maturation problems.

11. There is an unmet need for the treatment of uveitis in JIA, and this should be addressed in PIPs for JIA where appropriate. Specific data should be collected in all trials and especially in the long-term

follow-up studies addressing the occurrence of uveitis under treatment with the experimental agent.

12. There is a need for the standardisation of the PIP for JIA, and experts wished to contribute to this exercise.
13. It has been stressed the need to have an ethical requirement for pharmaceutical companies to continue providing the investigated treatment to patients enrolled in clinical trials until the drug is registered for use in JIA in that specific country.
14. There is a need to further discuss the issue of drugs directed against the same target (e.g. anti-TNF) to evaluate the possibility to simplify the regulatory requirements (e.g. PK/open label study followed by long term post marketing requirements)

FUTURE ACTION PLAN:

- The conclusions of the meeting will be presented to the PDCO and may be taken into consideration for the evaluation of new JIA PIPs.
- The draft of a standard PIP for chronic idiopathic arthritis will be developed,. After completion of the document it will be submitted to the, PDCO, and if adopted to the rheumatology working group with a possible proposal to amend the current EMA JIA guidelines.
- The responses from experts on juvenile animal studies will be forwarded to the non clinical working group of the PDCO, with a view to develop recommendations for the non clinical development for new active substances in JIA.
- The role and limits of extrapolation of efficacy will be analysed in detail and implemented in the standard PIP where applicable.
- A mechanism of implementation of safety concerns, and measures to address them within the PIP and post-authorisation pharmacovigilance measures, need to be further elaborated in co-operation by the PDCO, the CHMP, the rheumatology working party and the pharmacovigilance working party and learned societies and networks such as PRES and PRINTO.
- The possible involvement of the Agency in the development and steering of the registry of patients with JIA needs to be discussed and clarified. The PRES and PRINTO and PharmaChild should propose to the Agency the level and range of intended co-operation with regards to the registry.