Macedonian pharmaceutical bulletin, 68 (Suppl 1) 201 - 202 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.096
Short communication

Registration of medicinal products for pediatric use and Pediatric Investigation Plan

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Introduction

Regulation (EC) No 1901/2006, as amended (the 'Paediatric Regulation') lays down obligations, rewards and incentives for the development and placing on the market of medicines for use in children. The Paediatric Regulation set up some obligations for the applicant when developing a new medicinal product as well as new uses of an authorised product, in order to ensure that medicines to treat children are subject to ethical research of high quality and are appropriately authorised for use in children. The purpose is also to improve collection of information on the use of medicines in the various subsets of the paediatric population (EMA, 2021).

Pediatric regulation and PIP

The paediatric population covers the population between birth and the age of 17 years.
The Paediatric Regulation is consisted of:

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use;
- Regulation (EC) No 1902/2006, an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission.

Applications for marketing authorisation submitted to the European Medicines Agency (EMA) after 26 July 2008 must include the results of studies carried out as part of an agreed paediatric investigation plan (PIP) or information on a PIP deferral or waiver (EMA, 2021).

The Paediatric Regulation also foresees a paediatric-use marketing authorisation (PUMA) which is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed exclusively for use in the paediatric population.

The PUMA was introduced by the Paediatric Regulation for medicines that are:

- already authorised;
- no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC;
- to be exclusively developed for use in children.

The development of a PUMA must follow a paediatric investigation plan (PIP), which must be agreed by the Paediatric Committee (PDCO) (EMA, 2021a).

Applications for new indication(s), new pharmaceutical form(s) and/or new route(s) of administration must include one of the following documents/data in order to be considered 'valid':

- ✓ The results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP);
- ✓ EMA decision for a PIP including the granting of a deferral;
- ✓ EMA decision for granting a product-specific waiver;
- ✓ EMA decision for granting a class waiver (together with the Agency's confirmation letter of applicability if requested by the MAH).

The requirement for a PIP, PIP deferral or PIP waiver applies irrespective of the type of application submitted for such a change(s) i.e. variation or extension (or new

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marketing authorisation application) and irrespective of whether the change is related to adult or paediatric use.

The PIP should summarize relevant background information on the disease and medicinal product, and use this to justify a paediatric development programme that covers the entire paediatric population. Depending on the type of medicinal product and the relevance of the disease to the paediatric population, specific quality, safety, and/or efficacy measures may be proposed for all or part of the population. If measures are considered inappropriate for all or part of the paediatric population, then a waiver may be proposed but must be justified. If the paediatric development programme cannot be completed before submission of the adult application, then a deferral of the paediatric measures may be proposed but again this must be justified. In any case, a detailed timetable has to be provided and adhered to for any all measures being proposed.

If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee (EMA, 2021).

The PIP should be prepared in accordance with the "Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies.

Pediatric legislation in North Macedonia

In North Macedonia, the legislation does not recognize the term "medicinal product for pediatric use" as a separate entity. However, the current legislation foresees that all regulatory requirements for medicinal products intended for adult population are applicable for medicinal product for pediatric use (MALMED, 2007).

Conclusion

The development of a medicine requires that various studies be performed to ensure its quality, safety, and efficacy. These studies, in turn, require careful planning procedures so that they are ethically and scientifically valid. During the development process, a Paediatric Investigation Plan is written to ensure that all necessary data on the use of the medicine in children are obtained in the clinical studies in children. This is to ensure that the medicinal product that reaches the pediatric population is effective and safe.

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