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Inspections, Human Medicines Pharmacovigilance and Committees Division

PDCO monthly report of opinions on paediatric investigation plans and other activities

21-24 February 2017

Opinions on paediatric investigation plans

The Paediatric Committee (PDCO) adopted opinions agreeing paediatric investigation plans (PIPs) for the following medicines:

- Entolimod, EMEA-002020-PIP01-16, from Cleveland BioLabs Inc, for the treatment of acute radiation syndrome;
- rVSVΔG-ZEBOV-GP, EMEA-001786-PIP01-15, from Merck Sharp & Dohme (Europe) Inc., for the prevention of Ebola disease;
- Bempedoic acid, EMEA-001872-PIP01-15, from Esperion Therapeutics, Inc., for the treatment of elevated cholesterol;
- Olodaterol hydrochloride, EMEA-001965-PIP01-16, from Boehringer Ingelheim International GmbH, for the treatment of cystic fibrosis;
- Human fibrinogen concentrate, EMEA-001931-PIP01-16, from Biotest AG, for the treatment of congenital fibrinogen deficiency;
- Macimorelin, EMEA-001988-PIP01-16, from Aeterna Zentaris GmbH, for the diagnosis of growth hormone deficiency.

The PDCO adopted an opinion(s) on the **refusal** of a PIP, and a deferral for:

- Baclofen, EMEA-001549-PIP02-14, from Ethypharm, for the treatment of alcohol dependence.

For this medicine the PDCO granted a product-specific waiver on its own motion for all subsets of the paediatric population in the specified condition, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

A PIP sets out a programme for the development of a medicine in the paediatric population. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages. These data have to be submitted to the European Medicines Agency, or national competent authorities, as part of an application for a

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marketing authorisation for a new medicine, or for one covered by a patent. In some cases, a PIP may include a waiver of the studies in one or more paediatric subsets, or a deferral.

Opinions on product-specific waivers

The PDCO adopted positive opinions for product-specific waivers, recommending that the obligation to submit data obtained through clinical studies with children be waived in all subsets of the paediatric population, for the following medicines:

- Acetylsalicylic acid / Prasugrel HCl, EMEA-002071-PIP01-16, from Daiichi Sankyo Europe GmbH, for the prevention of thromboembolic events;
- Amlodipine / perindopril, EMEA-002091-PIP01-16, from CIPROS S.r.l., for the treatment of hypertension;
- Tobramycin, EMEA-000184-PIP03-16, from Novartis Europharm Limited, for the treatment of Pseudomonas aeruginosa pulmonary colonisation in patients with bronchiectasis;
- Candesartan / amlodipine, EMEA-002090-PIP01-16, from ERREKAPPA EUROTERAPICI S.p.A., for the treatment of hypertension.

Waivers can be issued if there is evidence that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Opinions on modifications to an agreed PIP

The PDCO also adopts, every month, opinions on modifications to an agreed PIP, which can be requested by the applicant when the plan is no longer appropriate or when there are difficulties that render the plan unworkable. The PDCO adopted positive opinions, agreeing change(s), for the following products:

- Recombinant human N-acetylglucosaminidase (rhNAGLU), EMEA-001653-PIP01-14-M02, from Alexion Europe SAS, for the treatment of Mucopolysaccharidosis IIIB (Sanfilippo B);
- Talimogene laherparepvec, EMEA-001251-PIP01-11-M03, from Amgen Europe B.V., for the treatment of solid malignant non-CNS tumours;
- Ustekinumab, EMEA-000311-PIP03-11-M02, from Janssen-Cilag International NV, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylarthritis and juvenile idiopathic arthritis);
- Evolocumab, EMEA-001268-PIP01-12-M04, from Amgen Europe B.V., for the treatment of elevated cholesterol and treatment of mixed dyslipidaemia;
- Trifarotene, EMEA-001492-PIP01-13-M01, from GALDERMA R&D, for the treatment of acne;
- Ibrutinib, EMEA-001397-PIP03-14-M02, from Janssen-Cilag International N.V., for the treatment of mature B-cell neoplasm;
- Oseltamivir phosphate, EMEA-000365-PIP01-08-M08, from Roche Registration Limited, for the treatment and prevention of influenza;
- Bivalent anti-human myostatin adnectin recombinant human IgG1-Fc fusion protein, EMEA-001793-

PIP01-15-M01, from Bristol-Myers Squibb International Corporation, for the treatment of Duchenne Muscular Dystrophy;

- Oritavancin diphosphate, EMEA-001270-PIP01-12-M01, from The Medicines Company, for the treatment of acute bacterial skin and skin structure infections;
- Letermovir, EMEA-001631-PIP01-14-M02, from Merck Sharp & Dohme (Europe), Inc., for the prevention of cytomegalovirus infection;
- Ivacaftor / lumacaftor, EMEA-001582-PIP01-13-M05, from Vertex Pharmaceuticals (Europe) Limited, for the treatment of cystic fibrosis;
- Rituximab, EMEA-000308-PIP01-08-M03, from Roche Registration Limited, for the treatment of autoimmune arthritis and treatment of diffuse large B-cell lymphoma;
- Siponimod hemifumarate, EMEA-000716-PIP01-09-M02, from Novartis Europharm Limited, for the treatment of multiple sclerosis;
- Lenvatinib, EMEA-001119-PIP02-12-M03, from Eisai Europe Ltd, for the treatment of osteosarcoma, treatment of follicular thyroid carcinoma and treatment of papillary thyroid carcinoma;
- Ferric maltol, EMEA-001195-PIP01-11-M02, from Shield TX (UK) Limited, for the treatment of iron deficiency anaemia (IDA);
- Posaconazole, EMEA-000468-PIP02-12-M03, from Merck Sharp & Dohme (Europe), Inc., for the Prevention of invasive fungal infections and Treatment of invasive fungal infections;
- Telaprevir, EMEA-000196-PIP01-08-M04, from Janssen-Cilag International NV, for the treatment of chronic hepatitis C; a product-specific waiver was granted for this medicine;
- Regorafenib, EMEA-001178-PIP01-11-M03, from Bayer Pharma AG, for the treatment of all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue).

Opinion on compliance check

The PDCO adopted a positive opinion on (full) compliance check for ipilimumab, EMEA-C-000117-PIP02-10-M07, from Bristol-Myers Squibb Pharma EEIG, for the treatment of melanoma.

A compliance check is performed to verify that all the measures agreed in a PIP and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Full compliance with all studies/measured contained in the PIP is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.

Before the submission of a request for a compliance check, applicants are encouraged to consult the Agency's Procedural advice for validation of a new marketing authorisation application or extension/variation application and compliance check with an agreed PIP.

Adoption of an opinion following re-examination

The PDCO adopted an opinion for the following product:

- Following the re-examination of the negative opinion on a modification of an agreed PIP adopted on 16 December 2016 for Methoxy polyethylene glycol-epoetin beta, EMEA-000172-PIP01-07-M02, from Roche Registration Limited, for the treatment of symptomatic anaemia associated with chronic

kidney disease, the PDCO maintained its opinion and recommended to refuse the changes proposed by the applicant regarding the paediatric investigation plan.

A re-examination of the opinion can be requested by the applicant within 30 days following receipt of the opinion of the PDCO. The grounds for the re-examination should be based only on the original information and scientific data provided in the application that were previously available to the PDCO and on which the initial opinion was based. This may include new analysis of the same data or minor protocol amendments to a previously proposed study. Significant changes to the previous plan cannot be part of the re-examination process.

Withdrawals

The PDCO noted that 5 applications were withdrawn during the late stages of the evaluation (30 days or less before completion of the procedure).

New meeting dates adopted

PDCO meeting dates for 2019-2021 were adopted during the PDCO February 2017 meeting. These dates are important for applicants in planning the submission of applications for PIPs, requests for waivers, requests for modification of an agreed PIP, and requests for compliance checks. The dates are published on the Agency's website at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/pdco_meetings_landing_page.jsp&mid=WC0b01ac0580028eaa

Other matters

The next meeting of the PDCO will be held on 21-24 March 2017.

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Notes:

1. As of 26 January 2009, pharmaceutical companies that submit an application for a marketing authorisation for a medicinal product, or those that submit an application for an extension of indication, a new route of administration, or a new pharmaceutical form of a medicinal product already authorised in the European Union, have to provide either the results of studies in children conducted in accordance with an approved PIP, or an Agency's decision on a waiver or on a deferral.

2. PDCO opinions on PIPs and waivers are transformed into Agency's decisions within the timeframe laid down by the Paediatric Regulation (Regulation (EC) No 1901/2006, as amended). The decisions can be found on the Agency's website at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d129

3. More information about the PDCO and the Paediatric Regulation is available in the Regulatory section of the Agency's website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cd

4. This meeting report, together with other information on the work of the Agency's, can be found on the Agency's website: http://www.ema.europa.eu

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